The Tricarboxylic Acid Cycle
(The Citric Acid Cycle)

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Second semester
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Three main pathways for energy production:
- Glycolysis
- Citric acid cycle
- Oxidative-Phosphorylation

Certain pathways are involved in both breakdown and buildup of molecules; these pathways are called amphibolic. The citric acid cycle is an example of this.

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Mitochondrion
- Outer membrane very permeable
- Inner membrane (cristae)
  - Permeable to pyruvate,
  - Impermeable to fatty acids, NAD, etc
- Matrix is inside inner membrane
Aerobic cells use a metabolic wheel – the citric acid cycle – to generate energy by acetyl CoA oxidation.

- A series of consecutive biochemical reactions catalyzed by enzymes that produce a specific end product.

Catabolism - the breakdown of food stuffs to simple organic chemicals.

Anabolism - the synthesis of biomolecules from simple organic chemicals.
Metabolism Summary

Proteins
- amino acids

Carbohydrates
- glucose, fructose, galactose

Fats and Lipids
- fatty acid, glycerol

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Urea Cycle
- urea

Citric Acid Cycle
- CO₂
- 2H⁺
- 2e⁻

Electron Transport Chain
- ATP
- ADP
- O₂
- H₂O

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Synthesis of glycogen

Glucose

Glucose-6-phosphate

Pentose phosphate pathway

Ribose, NADPH

Degradation of glycogen

Glycogen

Glycolysis

Gluconeogenesis

Ethanol

Pyruvate

Acetyl CoA

Fatty Acids

Amino Acids

Acetyl CoA

Fumarate

Succinate

Succinyl CoA

α-Ketoglutarate

Malate

Citrate

Oxaloacetate

The citric acid cycle is the final common pathway for the oxidation of fuel molecules — amino acids, fatty acids, and carbohydrates.

Most fuel molecules enter the cycle as acetyl coenzyme A.

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Three main pathways for energy production:

1- Glycolysis
2- Citric acid cycle
3- Oxidative-Phosphorylation

- Certain pathways are involved in both breakdown and buildup of molecules; these pathways are called **amphibolic**. The citric acid cycle is an example of this.

- Eight successive reaction steps.
- The six carbon citrate is formed from two carbon acetyl-CoA and four carbon oxaloacetate.
- Oxidation of citrate yields CO2 and regenerates oxaloacetate.
- The energy released is captured in the reduced coenzymes NADH and FADH2.
An Overview of the Citric Acid Cycle

- A four-carbon oxaloacetate condenses with a two-carbon acetyl unit to yield a six-carbon citrate.
- An isomer of citrate is oxidatively decarboxylated and five-carbon α-ketoglutarate is formed.
- α-ketoglutarate is oxidatively decarboxylated to yield a four-carbon succinate.
- Oxaloacetate is then regenerated from succinate.

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Three hydride ions (six electrons) are transferred to three molecules of NAD⁺, one pair of hydrogen atoms (two electrons) is transferred to one molecule of FAD.
1. **Citrate Synthase**

- Citrate formed from *acetyl CoA* and *oxaloacetate*
- Only cycle reaction with C-C bond formation

**Equation:**

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

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2. Aconitase

- Elimination of $\text{H}_2\text{O}$ from citrate to form $\text{C}=$ bond of *cis*-aconitate
- Stereospecific addition of $\text{H}_2\text{O}$ to *cis*-aconitate to form isocitrate

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3. Isocitrate Dehydrogenase

- Oxidative decarboxylation of isocitrate to a-ketoglutarate (a metabolically irreversible reaction)
- One of four oxidation-reduction reactions of the cycle
- Hydride ion from the C-2 of isocitrate is transferred to NAD\(^+\) to form NADH

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4. The $\alpha$-Ketoglutarate Dehydrogenase Complex

- Similar to pyruvate dehydrogenase complex
- Same coenzymes, identical mechanisms

$E_1$ - $\alpha$-ketoglutarate dehydrogenase (with TPP)
$E_2$ - dihydrolipoyl succinyltransferase (with flexible lipoamide prosthetic group)
$E_3$ - dihydrolipoyl dehydrogenase (with FAD)

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\[ \text{CH}_2 \text{COO}^{-} + \text{NAD}^+ + \text{CoA} \rightarrow \text{CH}_2 \text{COO}^{-} + \text{CO}_2 + \text{NADH} \]

$\alpha$-Ketoglutarate $\rightarrow$ Succinyl CoA
5. Succinyl-CoA Synthetase

- Free energy in thioester bond of succinyl CoA is conserved as GTP or ATP in higher animals (or ATP in plants, some bacteria)

- Substrate level phosphorylation reaction

\[
\text{GTP + ADP} \rightleftharpoons \text{GDP + ATP}
\]

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6. The Succinate Dehydrogenase Complex

- Complex of several polypeptides, an FAD prosthetic group and iron-sulfur clusters
- Embedded in the inner mitochondrial membrane
- Electrons are transferred from succinate to FAD and then to ubiquinone (Q) in electron transport chain
- Dehydrogenation is stereospecific; only the trans isomer is formed

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7. **Fumarase**

- Stereospecific *trans* addition of water to the double bond of *fumarate* to form *L-malate*

- Only the *L* isomer of malate is formed

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8. Malate Dehydrogenase

Malate is oxidized to form oxaloacetate.

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Stoichiometry of the Citric Acid Cycle

- Two carbon atoms enter the cycle in the form of acetyl CoA.
- Two carbon atoms leave the cycle in the form of CO₂.
- Four pairs of hydrogen atoms leave the cycle in four oxidation reactions (three molecules of NAD⁺ one molecule of FAD are reduced).
- One molecule of GTP, two molecules of water are consumed.
- 9 ATP (2.5 ATP per NADH, and 1.5 ATP per FADH₂) are produced during oxidative phosphorylation.
- 1 ATP is directly formed in the citric acid cycle.
- 1 acetyl CoA generates approximately 10 molecules of ATP.
Regulation of the Citric Acid Cycle

• **Pathway controlled by:**
  
  (1) Allosteric modulators
  (2) Covalent modification of cycle enzymes
  (3) Supply of acetyl CoA (pyruvate dehydrogenase complex)

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- **citrate synthase**
  (allosterically inhibited by NADH, ATP, succinyl CoA, citrate - feedback inhibition)

- **isocitrate dehydrogenase**
  (allostERIC effectors: (+) ADP; (-) NADH, ATP. Bacterial ICDH can be covalently modified by kinase/phosphatase)

- **α-ketoglutarate dehydrogenase complex**
  (inhibition by ATP, succinyl CoA and NADH)
Regulation of the citric acid cycle

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The citric acid cycle provides intermediates for biosyntheses.

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Net From Kreb’s

• Oxidative process
  – 3 NADH
  – 5 FADH₂
  – GTP
  – X2 per glucose
  – 6 NADH
  – 2 FADH₂
  – 2 GTP

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• All ultimately turned into ATP (oxidative phosphorylation)
Intermediates for Biosynthesis

The TCA cycle provides several of these

• $\alpha$-Ketoglutarate is transaminated to make glutamate, which can be used to make purine nucleotides, Arg and Pro
• Succinyl-CoA can be used to make porphyrins
• Fumarate and oxaloacetate can be used to make several amino acids and also pyrimidine nucleotides

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Regulation of the TCA Cycle

*Again, 3 reactions are the key sites*

- **Citrate synthase** - ATP, NADH and succinyl-CoA inhibit
  - Isocitrate dehydrogenase - ATP inhibits, ADP and NAD+ activate
  - α-Ketoglutarate dehydrogenase - NADH and succinyl-CoA inhibit, AMP activates

- Also note pyruvate dehydrogenase: ATP, NADH, acetyl-CoA inhibit, NAD+, CoA activate