OXIDATIVE CELLULAR METABOLISM:
KREB’S CYCLE AND ETC
The day mitochondria went from being "the powerhouse of the cell" to "the ATP synthesis by oxidative phosphorylation" was a horrible day.
Glycolysis
Fate of Pyruvate
Aerobic - Anaerobic

What Happens When the Cell Runs Out of O₂?

Pyruvate
(aerobic)
Krebs cycle

2NADH + 2H⁺

Glucose

2NAD⁺

2

CH₃

C=O

COO⁻

(anaerobic)

Lactate

Lactic Acid Cycle

H

CH₃

C-OH

COO⁻
Lactic Acid Pathway in Humans

• Some tissues better adapt to anaerobic conditions
  – RBCs do not contain mitochondria and **only** use the lactic acid pathway

• When ratio of oxygen supply to oxygen need falls below critical level

• **Oxygen debt**: The amount of energy required to return blood glucose levels back to normal and to replace glycogen reserves in muscle and liver
  – Skeletal muscle
    • Normal daily occurrence
    • Does not harm muscle tissue
  – Cardiac Muscle
    • Cardiac muscle normally respires aerobically
    • Myocardial ischemia occurs under anaerobic conditions
Cori Cycle

Lactic Acid to Glucose in the Liver
Anaerobic Metabolism Summary

• Final $e^-$ acceptor in anaerobic metabolism is pyruvic acid
• Lactic acid production in animal muscle occurs during oxygen debt
• Lactic acid needs to be produced so that NAD$^+$ can be regenerated to keep glycolysis going

Net ATP produced = 2 ATP
Intermediate Step

Pyruvic acid + Coenzyme A → Acetyl coenzyme A

NADH + H⁺

To Krebs Cycle
Kreb’s Cycle

- **Two** turns of the Krebs cycle are required for each mole of glucose
- At the end of the two turns, all of the original glucose molecule has been oxidized to $\text{CO}_2 + \text{H}_2\text{O}$
- Energy produced when bonds are broken is transferred to
  - 1 ATP
  - 3 NADH + H$^+$
  - 1 FADH$_2$
Kreb’s Cycle

Officer
Can
I
Keep
Selling
Sativa
For
Money
Electron Transport Chain

- The ETC is a series of complexes involved in redox reactions that transfer $2e^-$ from electron donors to electron acceptors.
- $2e^-$ are transferred between complexes by carrier proteins (CoQ and cyt c).
- The transfer of $2e^-$ is coupled to the pumping of $H^+$ ions from the matrix to the intermembrane space.
- The 4 complexes of the ETC are located in the inner membrane of the mitochondria.
- $O_2$ is the last molecule that accepts the $2e^-$ that entered the ETC.
- $O_2$ is reduced to $H_2O$. 
Summary of the steps of the ETC

NADH+H⁺ → Complex I → CoQ → Complex III → cytochrome c → Complex IV → H₂O
↑
Complex II
↑
Succinate
Electron Transport Chain

• NADH Dehydrogenase
  • Complex 1
    • $2e^-$ are donated from \textbf{NADH} + H$^+$
    • \textbf{NADH} + H$^+$ gets oxidized to NAD$^+$
    • $2e^-$ are accepted by FMN
    • FMN gets reduced
    • FMN donates $2e^-$ to CoQ
    • CoQ gets reduced to CoQH$_2$
    • CoQH$_2$ carries the $2e^-$ to Complex 3
  ❖ \textit{4H$^+$ get pumped into the intermembrane space}

• Succinate Dehydrogenase
  • Complex 2
    • $2e^-$ are donated from succinate
    • Succinate gets oxidized to fumarate
      • This is the same succinate that is the intermediate in the Kreb’s Cycle
    • $2e^-$ are accepted by FAD$^+$
    • FAD$^+$ gets reduced to FADH$_2$
    • FADH$_2$ donates $2e^-$ to CoQ
    • CoQ gets reduced to CoQH$_2$
    • CoQH$_2$ carries the $2e^-$ to Complex 3

\textit{Ubiquinone (CoQ)} is a carrier protein that moves through the membrane to deliver $2e^-$ to Complex 3
Electron Transport Chain

- **CoQ - Cytochrome c Reductase**
  - Complex 3
  - $2e^-$ are donated from CoQH$_2$
  - CoQH$_2$ gets oxidized to CoQ
  - Cytochrome c accepts $2e^-$
  - Cytochrome c gets reduced
  - Cytochrome c carries $2e^-$ to Complex 4

- **Complex 4**
  - $2e^-$ are donated from Complex 3 from Cytochrome c
  - $2e^-$ are accepted by Fe$^{3+}$
  - Fe$^{3+}$ gets reduced to Fe$^{2+}$
  - Fe$^{2+}$ donates $2e^-$ to Cytochrome a$_3$ – it gets reduced
  - Cytochrome a$_3$ gets oxidized when the electrons are accepted by O$_2$
  - O$_2$ gets reduced to H$_2$O

- **4H$^+$ get pumped into the intermembrane space**
Electron Transport Chain

- Summary of the flow of electrons through four complexes of the electron transport chain.
Electron Transport System

Oxidative Phosphorylation
Oxidative Phosphorylation

- Electron are being shuttled from glycolysis and the Kreb’s cycle by NADH + H⁺ and FADH₂
- NADH + H⁺ donates electrons to FMN
  - The result is the generation of 3 ATP for each pair of electrons
- FADH₂ donates electrons to CoQ
  - The result is the generation of 2 ATP for each pair of electrons
- Cytochrome a₃ transfers electrons to molecular oxygen to produce metabolic H₂O
  - Cytochrome a₃ is oxidized
  - Oxygen gets reduced

Oxidized NAD+ and FAD regenerated
The Final Electron Acceptor: Oxygen

• Oxygen functions as the final electron acceptor
  – Oxidizes cytochrome $a_3$

• Oxygen accepts 2 electrons

• $O_2 + 4H^+ \rightarrow 2H_2O$
Chemiosmosis

• Inner mitochondrial membrane allows transport of $\text{H}^+$ through respiratory assemblies
  – Respiratory assemblies contain a channel that permits the passage of $\text{H}^+$
  – Grouped into 3 proton pumps
  – Pumps $\text{H}^+$ from matrix into the intermembrane space
  – Creates a concentration gradient of $\text{H}^+$

• Phosphorylation is coupled to oxidation
  – $\text{H}^+$ passes through ATP Synthase which is a $\text{H}^+$ channel
  – Free energy released is used to make ATP
  – *Oxidative phosphorylation*
    • ADP and $\text{P}_i$ $\longrightarrow$ ATP
## Glucose Oxidation

<table>
<thead>
<tr>
<th>Step</th>
<th>ATP Produced</th>
<th>e⁻ carrier reduced</th>
<th>ATP produced</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Substrate-level phosphorylation</td>
<td>Oxidative phosphorylation</td>
<td></td>
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<tr>
<td><strong>Glycolysis</strong></td>
<td>2 ATP</td>
<td>2NADH + H⁺</td>
<td>6 ATP</td>
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<tr>
<td><strong>Intermediate Step</strong></td>
<td>2 ATP</td>
<td>2NADH + H⁺</td>
<td>6 ATP</td>
</tr>
<tr>
<td><strong>Kreb’s Cycle</strong></td>
<td>2 ATP</td>
<td>6NADH + H⁺</td>
<td>18 ATP</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>4 ATP</td>
<td></td>
<td>34 ATP</td>
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