Reading: Sec. 19.1 Electron-Transfer Reactions in Mitochondria (listed subsections only)

19.1.1 Electrons are Funneled to Universal Electron Acceptors  p. 692/709
19.1.2 Electrons Pass through a Series of Membrane-Bound Carriers  p. 693/710
19.1.3 Electron Carriers Function in Multi-enzyme Complexes  p. 696/712
19.1.4 The Energy of Electron Transfer is Efficiently Conserved in a Proton Gradient  p. 701/718


GENERAL FEATURES OF ELECTRON TRANSPORT MECHANISMS

The following apply to respiratory and photosynthetic e⁻ transport systems:

I. Electron transport involves an ordered sequence of coupled redox reactions. The electron carriers in this sequence exhibit a gradient of $\Delta E^o'$. Electrons move from carriers with relatively negative $\Delta E^o'$ to carriers with relatively positive $\Delta E^o'$. The free energy changes associated with these electron transfers can be calculated from:

$$\Delta G^o' = -\eta F \Delta E^o' = -(\# e^-)(96.5 \text{ kJ} \cdot \text{mol}^{-1}) (\Delta E^o_{\text{acceptor}} - \Delta E^o_{\text{donor}})$$

II. The electron carriers are "membrane associated" (i.e. integral membrane or peripheral membrane proteins or lipophilic carriers). Membrane association has made the structure and function of electron transport components more difficult to study than soluble enzymes.

III. Protein complexes with redox active prosthetic groups couple active transport of protons to the endergonic redox reactions of their electron carriers. Proton transport establishes an electrochemical gradient of protons across the membrane.

IV. Electrons are ultimately transferred to an external electron acceptor. O₂, NO₃⁻, SO₄²⁻, etc.
19.1.1 Electrons are Funneled to Universal Electron Acceptors

A surprisingly diverse array of redox active electron carriers are found in electron transport chains. Some are permanently bound to protein complexes (i.e. they are prosthetic groups), while others bind the protein complexes reversibly (i.e. they are co-substrates).

Be able to recognize the structures and know the essential properties of the following electron carriers:

<table>
<thead>
<tr>
<th>Electron Carrier</th>
<th>Type</th>
<th>Essential Properties</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAD(P)</td>
<td>co-substrate</td>
<td>H: hydride</td>
<td>Fig. 13-15</td>
</tr>
<tr>
<td>Flavins (FMN, FAD)</td>
<td>prosthetic group</td>
<td>$2e^- + 2H^+$</td>
<td>Fig. 13-18</td>
</tr>
<tr>
<td>Quinones</td>
<td>co-substrate</td>
<td>$1e^- + 1e^- + 1e^- + 2H^+$</td>
<td>Fig. 19-2</td>
</tr>
<tr>
<td>Heme</td>
<td>prosthetic group</td>
<td>$1e^-$</td>
<td>Fig. 19-3</td>
</tr>
<tr>
<td>Iron Sulfur Centers (FeS, Fe$_2$S$_2$, Fe$_4$S$_4$)</td>
<td>prosthetic group</td>
<td>$1e^-$</td>
<td>Fig. 19-5</td>
</tr>
<tr>
<td>Various metal ions, particularly Cu</td>
<td>prosthetic group</td>
<td>$1e^-$, ?</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: “Cytocromes” are proteins with redox-active heme groups.
“Flavoproteins” have flavin prosthetic groups

### Structural Comparison of Nucleotide-Based Redox Co-factors

- **Nicotinamide (NAD)**: Adenine - ribose - P - P - ribose - nicotinamide
- **FAD (Flavin-adenine dinucleotide)**: Adenine - ribose - P - P - ribose - flavin
- **FMN (Flavin mononucleotide)**: P - ribose - flavin
19.1.3 Electron Carriers Function in Multi-enzyme Complexes

**COMPLEX I**

Not responsible for details of internal structure as shown in Fig. 19-9

**COMPLEX II**

This is succinate dehydrogenase of Citric Acid cycle.

Not responsible for details of internal structure as shown in Fig. 19-10

**QUINONE**

**COMPLEX III** (=Cytochrome bc₁)

Not responsible for the details of the internal structure (Fig. 19-11) or for the details of the "Q Cycle" (Fig. 19-12).
**CYTOCHROME C**

"Soluble" in intermembrane space.
1 Heme

**COMPLEX IV (Cytochrome c Oxidase)**

Responsible for details:

- CuA;
- cyt a and cyt a3;
- CuB;
- 11 non-redox subunits
The 4 redox active groups in CytC oxidase are oxidized:

\[
\begin{align*}
\text{Cu} &= +2 \\
\text{Fe} &= +3 \\
\end{align*}
\]

2 molecules of CytC deliver 2 electrons that are passed through the complex to reduce Heme a3 and CuB.

Molecular oxygen binds and is reduced by 2 electrons, forming a peroxide bridge.

2 more electrons are provided by CytC which, along with 2 protons, reduces the peroxide bridge to hydroxyls.

Addition of 2 more protons releases 2 waters.
Proton Transport Account

Per Electron PAIR

<table>
<thead>
<tr>
<th></th>
<th>COMPLEX I</th>
<th>COMPLEX II</th>
<th>QUINONE</th>
<th>COMPLEX III</th>
<th>COMPLEX IV</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADH</td>
<td>4</td>
<td>-</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>FADH2</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

For each glucose there are:

- 10 NADH
- 2 FADH2
- TOTAL: 112 H^+ (for 100 H^+ and 12 H^+)

Evolutionary Perspectives

Many aspects of the interaction of organisms with O_2 can be rationalized by remembering that organisms evolved for several billion years in an atmosphere largely devoid of O_2. When O_2 appeared, it presented a challenge and an opportunity.

For example, metabolic reactions involving O_2 as a substrate (oxygenations) are uncommon generally, and virtually non-existent in the central (ancient) biochemical pathways. Where oxygenations do occur, they usually can be interpreted as comparatively recent.

Anaerobic respiration based on et chains featuring FeS proteins and Cytochromes antedated O_2 revolution. Fe was readily available then because of the solubility of ferrous ion. The O_2 Revolution made Fe less available. The challenge of acquiring sufficient iron for electron carriers was met by the evolution of a wide variety of chelation systems (siderophores) in many different lineages.
INHIBITORS and UNCOUPLERS

ET Inhibitors

See also Fig. 19-6.

<table>
<thead>
<tr>
<th>COMPLEX</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHIBITOR</td>
<td>Rotenone</td>
<td>Malonate</td>
<td>Antimycin A</td>
<td>Cyanide (CN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Azide N⁻³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CO</td>
</tr>
</tbody>
</table>

Malonate inhibition of Complex II (succinate dehydrogenase) is the classic example of competitive inhibition.

Uncouplers

Be sure you understand the concept of "coupling". It makes immediate sense that inhibiting electron transport (measured by O₂ consumption) would inhibit ATP synthesis. It is not so clear why the reverse (inhibiting ATP synthesis inhibits O₂ consumption) is also observed. That's coupling. The proton gradient is the physical basis of coupling.

Uncoupling means that oxygen consumption proceeds in the absence of ATP synthesis. This is possible when protons have an alternate route back into the mitochondrial matrix instead of passing through the ATP synthase.

Examples of experimental and natural uncoupling:

- 2,4-dinitrophenol (DNP); a H⁺ - a translocating ionophore (see below)
- Gramicidin - a small peptide that forms a transmembrane H⁺ channel
- Non-shivering thermogenesis in newborn and hibernating mammals involves activation of protein uncoupling agent in mitochondria-rich brown adipose tissue cells. (p. 717/736)

- A different form of uncoupling, in which electron transport does not involve proton pumping, occurs in Araceae inflorescence (BOX 19-1; p. 706/722)
ATP Synthase Inhibitors

Dicyclohexylcarbidoamide DCCD
Oligomycin B

These both specifically block proton flow through Fo.

Oligomycin