Respiratory electron transport

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**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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**Literature references**


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Reactome database release: 72

This document contains 2 pathways and 6 reactions (see Table of Contents)
Mitochondria are often described as the "powerhouse" of a cell as it is here that energy is largely released from the oxidation of food. Reducing equivalents generated from beta-oxidation of fatty acids and from the Krebs cycle enter the electron transport chain (also called the respiratory chain). During a series of redox reactions, electrons travel down the chain releasing their energy in controlled steps. These reactions drive the active transport of protons from the mitochondrial matrix, through the inner membrane to the intermembrane space. The respiratory chain consists of five main types of carrier; flavins, iron-sulfur centres, quinones, cytochromes (heme proteins) and copper. The two main reducing equivalents entering the respiratory chain are NADH and FADH2. NADH is linked through the NADH-specific dehydrogenase whereas FADH2 is reoxidised within succinate dehydrogenase and a ubiquinone reductase of the fatty acid oxidation pathway. Oxygen is the final acceptor of electrons and with protons, is converted to form water, the end product of aerobic cellular respiration. A proton electrochemical gradient (often called protonmotive force) is established across the inner membrane, with positive charge in the intermembrane space relative to the matrix. Protons driven by the proton-motive force, can enter ATP synthase thus returning to the mitochondrial matrix. ATP synthases use this exergonic flow to form ATP in the matrix, a process called chemiosmotic coupling. A by-product of this process is heat generation.

An antiport, ATP-ADP translocase, preferentially exports ATP from the matrix thereby maintaining a high ADP:ATP ratio in the matrix. The tight coupling of electron flow to ATP synthesis means oxygen consumption is dependent on ADP availability (termed respiratory control). High ADP (low ATP) increases electron flow thereby increasing oxygen consumption and low ADP (high ATP) decreases electron flow and thereby decreases oxygen consumption. There are many inhibitors of mitochondrial ATP synthesis. Most act by either blocking the flow of electrons (eg cyanide, carbon monoxide, rotenone) or uncoupling electron flow from ATP synthesis (eg dinitrophenol). Thermogenin is a natural protein found in brown fat. Newborn babies have a large amount of brown fat and the heat generated by thermogenin is an alternative to ATP synthesis (and thus electron flow only produces heat) and allows the maintenance of body temperature in newborns.

The electron transport chain is located in the inner mitochondrial membrane and comprises some 80 proteins organized in four enzymatic complexes (I-IV). Complex V generates ATP but has no electron transfer activity. In addition to these 5 complexes, there are also two electron shuttle molecules; Coenzyme Q (also known as ubiquinone, CoQ) and Cytochrome c (Cytc). These two molecules shuttle electrons between the large complexes in the chain.

How many ATPs are generated by this process? Theoretically, for each glucose molecule, 32 ATPs can be produced. As electrons drop from NADH to oxygen in the chain, the number of protons pumped out and returning through ATP synthase can produce 2.5 ATPs per electron pair. For each pair donated by FADH2, only 1.5 ATPs can be formed. Twelve pairs of electrons are removed from each glucose mo-
lecule;
10 by NAD+ = 25 ATPs
2 by FADH2 = 3 ATPs.

Making a total of 28 ATPs. However, 2 ATPs are formed during the Krebs' cycle and 2 ATPs formed during glycolysis for each glucose molecule therefore making a total ATP yield of 32 ATPs. In reality, the energy from the respiratory chain is used for other processes (such as active transport of important ions and molecules) so under conditions of normal respiration, the actual ATP yield probably does not reach 32 ATPs.

The reducing equivalents that fuel the electron transport chain, namely NADH and FADH2, are produced by the Krebs cycle (TCA cycle) and the beta-oxidation of fatty acids. At three steps in the Krebs cycle (isocitrate conversion to oxoglutarate; oxoglutarate conversion to succinyl-CoA; Malate conversion to oxaloacetate), a pair of electrons (2e-) are removed and transferred to NAD+, forming NADH and H+. At a single step, a pair of electrons are removed from succinate, reducing FAD to FADH2. From the beta-oxidation of fatty acids, one step in the process forms NADH and H+ and another step forms FADH2.

Cytoplasmic NADH, generated from glycolysis, has to be oxidized to reform NAD+, essential for glycolysis, otherwise glycolysis would cease to function. There is no carrier that transports NADH directly into the mitochondrial matrix and the inner mitochondrial membrane is impermeable to NADH so the cell uses two shuttle systems to move reducing equivalents into the mitochondrion and regenerate cytosolic NAD+.

The first is the glycerol phosphate shuttle, which uses electrons from cytosolic NADH to produce FADH2 within the inner membrane. These electrons then flow to Coenzyme Q. Complex I is bypassed so only 1.5 ATPs can be formed per NADH via this route. The overall balanced equation, summing all the reactions in this system, is

\[ \text{NADH (cytosol)} + \text{H}^+ (\text{cytosol}) + \text{NAD}^+ (\text{mito.}) = \text{NAD}^+ (\text{cytosol}) + \text{NADH (mito.)} + \text{H}^+ (\text{mito.}) \]

The malate-aspartate shuttle uses the oxidation of malate to generate NADH in the mitochondrial matrix. This NADH can then be fed directly to complex I and thus can form 3 ATPs via the respiratory chain. The overall balanced equation is

\[ \text{NADH (cytosol)} + \text{H}^+ (\text{cytosol}) + \text{FAD} (\text{inner memb.}) = \text{NAD}^+ (\text{cytosol}) + \text{FADH2 (inner memb.)} \]

Both of these shuttle systems regenerate cytosolic NAD+.

The entry point for NADH is complex I (NADH dehydrogenase) and the entry point for FADH2 is Coenzyme Q. The input of electrons from fatty acid oxidation via ubiquinone is complicated and not shown in the diagram.

**Literature references**


## Editions

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Complex I biogenesis

**Location:** Respiratory electron transport

**Stable identifier:** R-HSA-6799198

Complex I (NADH:ubiquinone oxidoreductase or NADH dehydrogenase) utilises NADH formed from glycolysis and the TCA cycle to pump protons out of the mitochondrial matrix. It is the largest enzyme complex in the electron transport chain, containing 45 subunits. Seven subunits (ND1-6, ND4L) are encoded by mitochondrial DNA, the remainder encoded in the nucleus. The enzyme has a FMN prosthetic group and 8 Iron-Sulfur (Fe-S) clusters. The subunits are assembled together in a coordinated manner via pre-assembled subcomplexes to form the mature holoenzyme. The so-called "assembly factor" proteins, acting intrinsically or transiently, are required for constructing complex I although their exact roles in the biogenesis are not fully understood (Fernandez-Vizarra et al. 2009, Mckenzie & Ryan 2010, Mimaki et al. 2012, Andrews et al. 2013).

**Literature references**


**Editions**

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Complex I oxidises NADH to NAD+, reduces CoQ to QH2

**Location:** Respiratory electron transport

**Stable identifier:** R-HSA-163217

**Type:** transition

**Compartments:** mitochondrial inner membrane

Complex I (NADH:ubiquinone oxidoreductase or NADH dehydrogenase) utilizes NADH formed from glycolysis and the TCA cycle to pump protons out of the mitochondrial matrix. It is the largest enzyme complex in the electron transport chain, containing 45 subunits. Seven subunits (ND1-6, ND4L) are encoded by mitochondrial DNA (Loeffen et al. [1998]), the remainder are encoded in the nucleus. The enzyme has a FMN prosthetic group and 8 Iron-Sulfur (Fe-S) clusters. The electrons from NADH oxidation pass through the flavin (FMN) and Fe-S clusters to ubiquinone (CoQ). This electron transfer is coupled with the translocation of protons from the mitochondrial matrix to the intermembrane space. For each electron transferred, 2 protons can be pumped out of the matrix. As there are 2 electrons transferred, 4 protons can be pumped out.

Complex I is made up of 3 sub-complexes - Iron-Sulfur protein fraction (IP), Flavoprotein fraction (FP) and the Hydrophobic protein fraction (HP), probably arranged in an L-shaped structure with the IP and FP fractions protruding into the mitochondrial matrix and the HP arm lying within the inner mitochondrial membrane. The overall reaction can be summed as below:

\[
\text{NADH + Ubiquinone + 5H}^+ \text{ (mito. matrix) = NAD}^+ + \text{Ubiquinol + 4H}^+ \text{ (intermemb. space)}
\]

The electrons from complex I are transferred to ubiquinone (Coenzyme Q, CoQ), a small mobile carrier of electrons located within the inner membrane. Ubiquinone is reduced to ubiquinol (QH2) during this process.

Mitochondrial coenzyme Q-binding protein COQ10 homologs A and B (COQ10A and B) are thought to be required for correct coenzyme CoQ in the respiratory chain. Their function in humans is unknown but the yeast model suggests functions in facilitating de novo CoQ biosynthesis and in delivering it to one or more complexes of the respiratory electron transport chain (Barros et al. 2005, Allan et al. 2013).

**Followed by:** Electron transfer from ubiquinol to cytochrome c of complex III
**Literature references**


**Editions**

2005-05-10  
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Jassal, B.
Transfer of electrons through the succinate dehydrogenase complex

**Location:** Respiratory electron transport

**Stable identifier:** R-HSA-163213

**Type:** transition

**Compartments:** mitochondrial inner membrane

**Inferred from:** Transfer of electrons through the bovine succinate dehydrogenase complex (Bos taurus)

This event is deduced on the basis of bovine experimental data.

Complex II (succinate dehydrogenase) transfers electrons from the TCA cycle to ubiquinone. The 6th step in the TCA cycle is where succinate is dehydrogenated to fumarate with subsequent reduction of FAD to FADH2. FADH2 provides the electrons for the transport chain. Succinate dehydrogenase belongs to subclass 1 of the SQR family (succinate:quinone reductase) (classified by Hagerhall, C and Hederstedt, L [1996]).

It consists of 4 subunits (referred to as A, B, C and D), all nuclear-encoded and is located on the matrix side of the inner mitochondrial membrane. Subunits A and B are hydrophilic whereas subunits C and D are integral proteins of the inner membrane. SQRs usually contain 3 Fe-S clusters bound by the B subunit. Succinate dehydrogenase contains one [2Fe-2S] cluster, one [4Fe-4S] cluster and one [3Fe-4S] cluster. Additionally, the A subunit has a covalently-bound FAD group. Reduced complex II has this FAD converted to FADH2. The electrons from complex II are transferred to ubiquinone (also called Q, Coenzyme Q or CoQ), a small mobile carrier of electrons located within the inner membrane. Ubiquinone is reduced to ubiquinol during this process.

The mitochondrial heat shock protein 75 kDa (TRAP1) inhibits Complex II of the respiratory chain which elicits respiratory downregulation, leading to a pseudohypoxic state. This state is caused by succinate-dependent HIF1-alpha stabilisation which, in turn, can promote tumorigenesis (Sciacovelli et al. 2013, Yoshida et al. 2013, Guzzo et al. 2014).

**Followed by:** Electron transfer from ubiquinol to cytochrome c of complex III
Literature references


Editions

2005-06-10 Authored Jassal, B.
Reducing equivalents from beta-oxidation of fatty acids transfer to ETF

**Location:** Respiratory electron transport

**Stable identifier:** R-HSA-169260

**Type:** transition

**Compartments:** mitochondrial matrix

Electron transfer flavoprotein (ETF) is a 63kDa heterodimer composed of alpha and beta subunits and binds one FAD and one AMP per dimer. ETF resides on the matrix face of the mitochondrial inner membrane. Reducing equivalents from the beta-oxidation of fatty acyl CoAs are transferred to ETF, reducing the ETF-bound FAD to FADH2 (Wood 1999).

**Followed by:** ETFDH oxidises ETF (reduced) to ETF, reduces CoQ to QH2

**Literature references**

ETFDH oxidises ETF (reduced) to ETF, reduces CoQ to QH2

**Location:** Respiratory electron transport

**Stable identifier:** R-HSA-169270

**Type:** transition

**Compartments:** mitochondrial matrix, mitochondrial inner membrane

ETF-ubiquinone oxidoreductase (ETFDH), catalyses the re-oxidation of reduced ETF, with ubiquinone (CoQ) as the electron acceptor being reduced to ubiquinol (QH2) (Estornell et al. 1992, MacLennan et al. 1997).

**Preceded by:** Reducing equivalents from beta-oxidation of fatty acids transfer to ETF

**Followed by:** Electron transfer from ubiquinol to cytochrome c of complex III

**Literature references**


Electron transfer from ubiquinol to cytochrome c of complex III

Location: Respiratory electron transport

Stable identifier: R-HSA-164651

Type: transition

Compartments: mitochondrial inner membrane

The protonmotive Q cycle is the mechanism by which complex III transfers electrons from ubiquinol to cytochrome c, linking this process to translocation of protons across the membrane. This cycle is complicated by the fact that both ubiquinol is oxidised and ubiquinone is reduced during this process. Through a complex series of electron transfers, Complex III consumes two molecules of ubiquinol (QH2) and two molecules of oxidized cytochrome c, generates one molecule of ubiquinone (Q) and two molecules of reduced cytochrome c, regenerates one molecule of ubiquinol (QH2), and mediates the translocation of two protons from the mitochondrial matrix to the mitochondrial intermembrane space. The overall reaction can be summed up as

\[2\text{QH}_2 + 2\text{cyt c (ox.)} + \text{Q} + 2\text{H}^+ \text{(matrix)} = 2\text{Q} + 2\text{cyt c (red.)} + \text{QH}_2 + 4\text{H}^+ \text{(intermemb. space)}\]

**Preceded by:** Complex I oxidises NADH to NAD+, reduces CoQ to QH2, Transfer of electrons through the succinate dehydrogenase complex, ETFDH oxidises ETF (reduced) to ETF, reduces CoQ to QH2

**Followed by:** Electron transfer from reduced cytochrome c to molecular oxygen

**Literature references**


**Editions**

2005-06-14  Authored  Jassal, B.
Electron transfer from reduced cytochrome c to molecular oxygen

Location: Respiratory electron transport

Stable identifier: R-HSA-163214

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial intermembrane space, mitochondrial matrix

Complex IV (COX, cytochrome c oxidase) contains the hemeprotein cytochrome a and a3. It also contains copper atoms which undergo a transition from Cu+ to Cu2+ during the transfer of electrons through the complex to molecular oxygen. A bimetallic centre containing a copper atom and a heme-linked iron protein binds oxygen after 4 electrons have been picked up. Water, the final product of oxygen reduction, is then released. Oxygen is the final electron acceptor in the respiratory chain. The overall reaction can be summed as

\[
4\text{Cyt c (red.)} + 12\text{H}^+ (\text{in}) + \text{O}_2 = 4\text{Cyt c (ox.)} + 2\text{H}_2\text{O} + 8\text{H}^+ (\text{out})
\]

Four protons are taken up from the matrix side of the membrane to form the water (scalar protons). Wikstrom (1977) suggests 4 protons are additionally transferred out from the matrix to the intermembrane space.

COX ancillary proteins mediate membrane insertion, catalytic core processing, copper transport and insertion into core subunits and heme A biosynthesis (Stilburek et al. 2006, Fontanesi et al. 2006, Soto et al. 2012). To date, all Mendelian disorders presenting COX deficiency have been assigned to mutations in ancillary factors, with the exception of an infantile encephalomyopathy caused by a defective COX6B1 and an exocrine pancreatic insufficiency caused by a defective COX4I2 gene (Soto et al. 2012). Balsa et al have shown that NDUFA4, formerly considered to be a constituent of NADH dehydrogenase (Complex I), is instead a component of the cytochrome c oxidase (CIV) (Balsa et al. 2012). Patients with NDUFA4 mutations display COX deficiencies (Pitceathly et al. 2013).

Preceded by: Electron transfer from ubiquinol to cytochrome c of complex III
Literature references


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