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Biochemistry

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Doctor

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In the previous lecture we came across the 3 major concepts of oxidative phosphorylation:

Flow of electrons down the chain → Pumping protons from matrix to the intermembrane space against their electrochemical gradient → Flow of protons to the matrix down the gradient, through ATP synthase and production of ATP.

Now we will talk about the details of each step:

Electron Transport Chain

General concept of the process: There are complexes in the inner mitochondrial membrane (proteins, enzymes, electron carriers) that alternate between their reduced and oxidized states as they accept and then donate electrons. Each component of the chain becomes reduced when it accepts electrons from its "uphill" neighbor, which has a lower affinity for electrons (lower reduction potential). It then returns to its oxidized form as it passes electrons to its "downhill" neighbor (higher reduction potential). We can conclude that electron movement is governed by difference in reduction potential, in other words (**change in energy**). This energy will be utilized to pump (pump=consuming energy) protons against their gradient. Pumping of protons increase the gradient of protons until it reaches a point where the change in energy is not enough to pump protons against the electrochemical gradient any more.

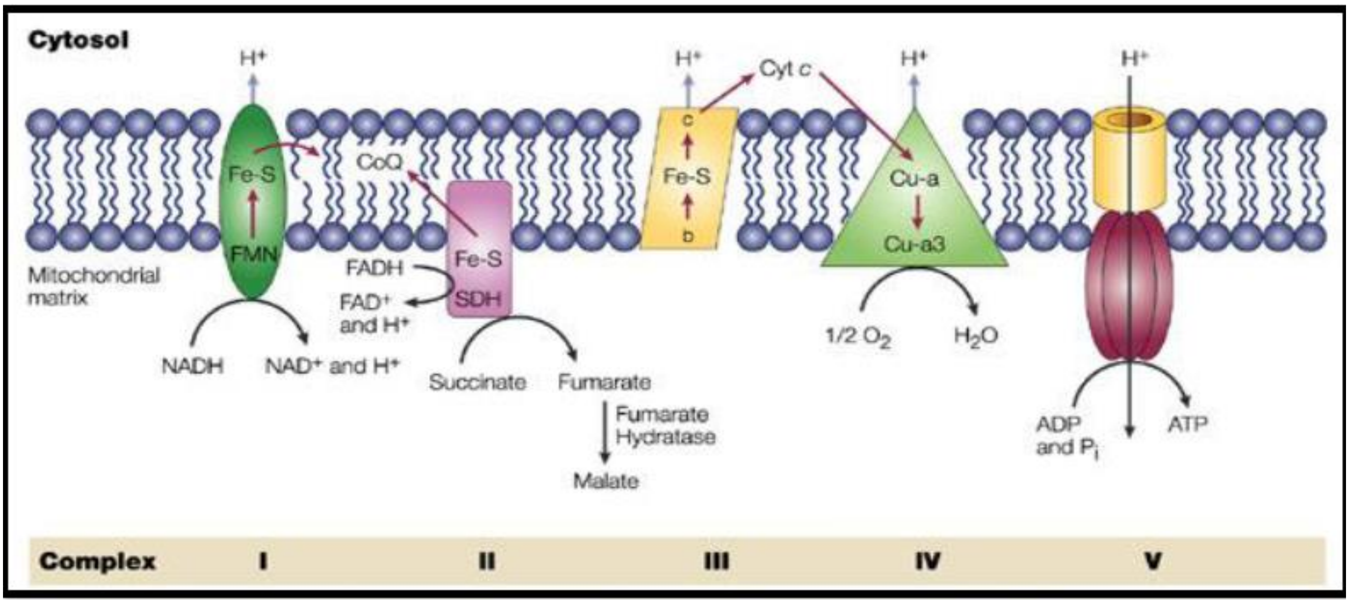
Now, what are the sources of electrons?

1 – NADH which is generated from TCA and Glycolysis and Pyruvate dehydrogenase. NADH is found free in the solution of the matrix and carries two electrons in the form of hydride ions.

2 – FADH2 which is generated from TCA. It is bound to succinate dehydrogenase (enzyme in the TCA that is embedded in the inner mitochondrial membrane and it also forms complex 2 of the ETC) and carries two electrons in the form of two hydrogen.

Organization of the Chain

The inner mitochondrial membrane contains four separate protein complexes **(I, II, III, IV).** These proteins are enzymes, each one of them contains a special prosthetic group (metals, heme group) or coenzyme (FAD, FMN) that allows it to work as oxidoreductase (accept and donate electrons).



Journey of electrons that come from NADH:

NADH → complex I → CoQ → complex III → cytochrome C → complex IV → O2

Complex I: It has 3 names, **complex 1** as it is the first acceptor of electrons, **NADH dehydrogenase** as it oxidizes NADH and takes its two electrons in the form of hydride ions, **NADH CoQ Oxidoreductase**. Complex I has a tightly bound molecule of flavin mononucleotide (FMN) that allows it to work as oxidoreductase. FMN accepts the two hydrogen atoms holding the electrons, becoming FMNH2. FMNH2 passes the 2 electrons to clusters of iron-sulfur (Fe-S) complex (there are 7 in the complex). Fe-S can carry one electron at a time until the two electrons are at the surface of Complex 1 and now they are ready to be picked up.

In order for the two electrons to reach complex 3 they must move through the lipid environment of the membrane. Electrons alone can not do that, so they require a carrier that is **Coenzyme Q or Ubiquinone.** CoQ is a lipid-soluble quinone that has a hydrophobic part to move through the membrane and a small hydrophilic part to carry electrons with it. It carries two electrons to complex III.

Before we continue the journey of the two electrons, we must talk about a protein known as cytochrome. Most of the remaining electron carriers between CoQ and oxygen are proteins called **cytochromes.** Their prosthetic group, called a heme group, has an iron atom that accepts and donates electrons. (The heme group in a cytochrome is similar to the heme group in hemoglobin, the protein of red blood cells, except that the iron in hemoglobin carries oxygen, not electrons.) The electron transport chain has several types of cytochromes, each named "cyt" with a letter and number to distinguish it as a different protein with a slightly different electron-carrying heme group. The heme group must work in electron transfer to call the protein cytochrome. The general structure of heme is composed of 4 pyrrole rings connected to each other forming large porphyrin ring. Each pyrrole ring contains a nitrogen atom that forms a bond with Fe. They are classified according to type of side chains that are attached to the porphyrin ring. Different side chain results in different type of attachment to proteins and different light absorbance.

Complex 3: it has another two names**, Cytochrome bc1** as it contains b and c1 heme group**, CoQ cytochrome c oxidoreductase**. Complex 3 can work as oxidoreductase because it contains heme (b and c1) and Fe-S cluster. Heme B accepts the electron and move it to Fe-S then from Fe-S they move to heme C1 **(CoQ → B → Fe-S→ c1)**. From c1 electrons are picked up by **Cytochrome C** which is found in the intermembrane space and can carry one electron so more than one will transport electrons to complex 4.

Complex IV (4): it has another name, Cytochrome a+a3 as it contains heme a and a3. This enzyme works as oxidoreductase because it contains 4 prosthetic groups (2 Heme and 2 cupper Cu), Heme a is connected with CuA **(CuA-a)** and Heme a3 is connected to CuB **(CuB-a3)**. The Iron of last Heme group (a3) is converted from the ferric state (oxidized, Fe+++) to ferrous state (reduced, Fe++) so oxygen now can bind iron. Four electrons are required to reduce one molecule of O+2 to two molecules of H2O.

Journey of electrons that come from FADH2:

FADH2 → complex II → CoQ → complex III → cytochrome C → complex IV → O2

Complex II (succinate dehydrogenase):

As we know, FADH2 must stay bound to an enzyme or a compound and can't be found free in the solution. So how it enters the ETC?

FADH2 is produced when succinate is converted to fumarate in TCA, the enzyme that catalyzes this reaction is succinate dehydrogenase. Succinate dehydrogenase is embedded in the membrane as part of the ETC. So when FADH2 is produced, it directly gives the two electrons to Fe-S cluster (Fe-S is also found in the enzyme). Electrons then move to CoQ and continue the journey.

NOTE: ETC has two entry points: complex 1 and 2, one form electrons of NADH and the other for FADH2.

Pumping protons.

As we said before: electron movement is governed by difference in reduction potential, in other words (change in energy). This energy will be utilized to pump (pump=consuming energy) protons against their gradient (chemical and electrical). Pumping of protons increase the gradient of protons until it reaches a point where the change in energy is not enough to pump protons any more.

As electrons flow through **complex 1 to CoQ** the released energy is used to pump **4** protons across the inner mitochondrial membrane to the intermembrane space. The same for **complex 3 to cytochrome c. 2 protons** are pumped when electrons move from **complex 4 to oxygen. Net = 10 protons for each NADH molecule.**

In the case of FADH2 no protons are pumped at complex 2 because the energy released from movement of electrons from complex 2 to CoQ is not enough (almost zero) to pump protons. **Net= 6 protons for each FADH2 molecule.**

For each 4 protons moving down their electrochemical gradient through ATP synthase 1 molecule of ATP will be produced from ADP and inorganic phosphate. This means that one NADH gives 2.5 ATP and one FADH2 gives 1.5 ATP. In another way, we can say that each 2 NADH give 5 ATP and each 2 FADH2 give 3 ATP.

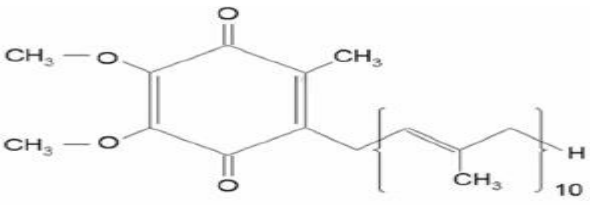
Types of electron transfer through ETC:

1 – Direct movement in the form of electrons such as in HEME and METALS

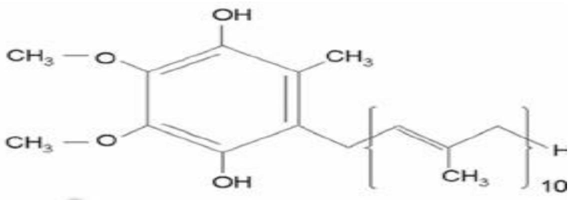
2 – Movement in the form of hydride ion such as in NADH, NADPH

3 – Movement in the form of hydrogen such as FADH2, FMNH2

Ubiquinone as electron carrier



Ubiquinone



Ubiquinol

Ubiquinone: (one = ketone group and there are two in the structure, quin= cyclic diene structure). This molecule can carry 2 electrons. Each electron is added by reduction of one ketone group to hydroxyl group. if the molecule has one ketone group and one hydroxyl group, it is referred as semi-oxidized or semi-reduced.

The molecule is also called coenzyme Q. It is a lipid-soluble benzoquinone with along ***isoprenoid*** side chain. It can accept either one or two electrons so it acts as a junction a 2-electron donor and 1-electron acceptor. Sometimes prescribed for recovering MI patient.

Finally, the oxidative phosphorylation requires:
1 – electron source

2 – electron acceptor

3 – electron carrier

4 – enzymes and coenzymes

5 – atp synthase

6- Intact membrane that separate protons to establish the difference in gradient.