SHEET NO.
6

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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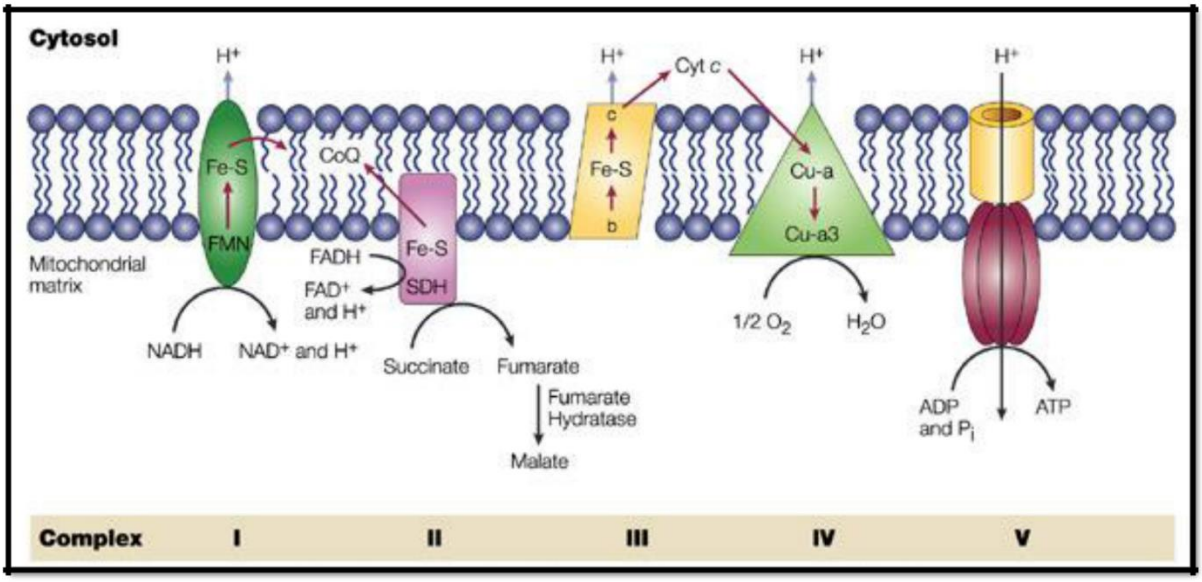
Oxidative phosphorylation (OxPhos)



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 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.)

Journey of electrons that come from NADH:

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

1) 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.

2) CoQ: Electrons alone cannot 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****. You should know that heme proteins are divided into 3 classes, depending on the heme function in the protein:*
a-**binding heme**, similar to the heme group in hemoglobin, the protein of red blood cells, and also myoglobin as another example.
b-**catalyst heme**, where the role of iron and heme to catalyse reactions, without accept or releasing electrons.
c-**heme as electron carrier**, which accepts and donates electrons (whether it is catalyst in the same time or anything else), we call it cytochrome.

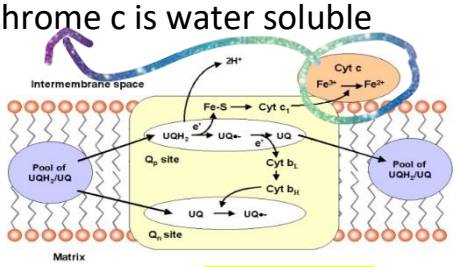
Now, most of the remaining electron carriers between CoQ and oxygen are proteins called cytochromes. Their prosthetic group, called a heme group, has an iron atom that accepts and donates electrons. (The heme group in a cytochrome is, except that the iron in hemoglobin carries oxygen, not electrons.) 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.
(what is highlighted in yellow is the only thing that you need to focus on from this long paragraph 😊)

3)Complex 3: it has another two names, **Cytochrome bc1** as it contains 2 hemes of type b (one is shown in the picture, while the other is hidden aside) and one of type c1 heme group, and also called **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.

Let get a bit closer: CoQ → complex III- (Q cycle)

This cycle Q is divided into two mini ones:

a-The first mini cycle is when **coenzyme Q** carries two electrons from NADH or $FADH_2$,it gets reduced. It carries them as QH_2 (2 electrons in the form of 2 hydrogen), the tow hydrogen molecules will pass towards the intermembrane space, releasing the two electrons to complex 3. the first electron passes to first **b heme group** then to the iron sulfur center then to cytochrome c1(the heme group in complex 3) and finally to **cytochrome c,** cytochrome c is water soluble protein attached to interspace side of complex 3, when it grabs electron it will be reduced and detached from complex 3 to complex 4, and get oxidized so will be back to complex 3 and so on. while the second electron can't pass the same route, because cytochrome c has only one heme group (one iron),and can reduced by just one electron (fe^{+3}→fe^{+2}). So instead, it passes down the complex toward the matrix and binds to b heme group (also called cyt b), which is located closer to the inner side mitochondrial membrane.



Now, what we have? The CoQ donated the both electrons and became oxidized ,so it will detach complex 3, and binds to the lower part of it, where there is the b heme group, which have high affinity to oxidized CoQ ,oxidized CoQ binds finally to electron that passed to lower b heme group and getting to be semi-oxidized CoQ.

b-The second mini cycle is when another reduced CoQ comes and binds to the upper part of complex 3, where it has high affinity to electrons, one electron will pass to **cytochrome c** ,and the other one will go down and binds to oxidized CoQ , and that's how another reduced CoQ molecule is regenerated.

Summary: 4 electrons come by two molecules of CoQ, two electons pass and two ones are regenerated bound to one CoQ, which enters the followd cycle, and that should explain why 2 electrons pass to complex 4 each cycle while we have 4 electrons.

4- Complex IV (4): it has another name, **cytochrome c-oxidize** because it oxidizes **cytochrome c** in the presence of O_2. 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). When cyt c donates the electron, it will be shared between (CuA-a), because the cupper has one oxidation state: (Cu+2→Cu+1), and also the iron (Fe+3→Fe+2), thus it will be shared. Then it will continue to (CuB-a3) and will be shared between them. Another electron will pass the same route so we will have 2 electrons, one electron reduces CuB, and the other reduces Heme group (a3), converted from the ferric state (oxidized, Fe^{+3}) to ferrous state (reduced, Fe^{+2}). So then oxygen (O^{+2}) which has high affinity to complex 4 since the heme is reduced, enters and gets reduced by the 2 electrons, and this is why we actually reduce the electrons. Four electrons are required to reduce one molecule of O_2 two molecules of H2O.
$O_2+H_2 \rightarrow H_2O$

Why do we need oxygen?

first of all, keeps in your mind that when we mention oxygen in metabolism, it always goes with CO, weather you want to talk about the toxicity of CO or its pathway, it binds where the oxygen binds. But CO_2 is coupled with O_2 only in lungs, where O2 will be in and CO2 is out. In other place in the body, they function in different manner.CO2 will be dissolved in the blood as bicarbonate, and some will be binds to 3 in terminus of hemoglobin producing the carbonate molecule. But when we are talking about mitochondria, CO_2 gets out of Krebs cycle and we exhale it. While O2 binds to iron of the heme, and it goes inside the oxidative phosphorylation process into ECF, and it gets bound to complex 4 since it has reduced heme, and so O2 gets reduced to H_2O. thus,most of O_2 that we breath in, it gets converted to water, and that's how we keep the water in the body within certain percentage (homeostasis).

5)Pumping protons (back to slide 18)

What motivates electron to move between complexes?

The Difference in redox potential (ΔE) between complexes, accordingly there will be difference in the free energy (ΔG), this energy will be employed to pump H^+ out of the mitochondrial **matrix** across the inner membrane and into the **intermembrane** space.

a-There will be 10 (H^+) molecules that will be pumped, by the electrons transfer from NADH to O_2 :

energy difference provided by transfer of 2 electrons between X to B.	between complex 1 to CoQ	between complex 3 to cytC	between complex 4 to O2
this extra energy invests how much protons to be pumped out	4 protons	4 protons	2 protons

b- There will be 6 (H^+) molecules that will be pumped, by the electron transfer from $FADH_2$ to O_2 :

energy difference provided by transfer of 2 electrons between X to B.	between complex 2 to CoQ	between complex 3 to cytC	between complex 4 to O2
this extra energy invests how much protons to be pumped out	0 protons because there will be no enough energy difference to pump protons when FADH2 donates electrons to CoQ. that's why complex 2(succinate dehgrogenase) doesn't spanning the inner membrane, because it wont pump protons>	4 protons	2 protons

*Conclusion: the energy available from NADH is higher compared to $FADH_2$.

6) ATPase: protons aren't allowed to enter the matrix from outside, so they start pressurizing on membrane, producing electrochemical gradient, as this gradient increase and increase, there is a link that allows protons to pass called **ATP synthase**, and this according to their gradient and energy difference, this(ΔG) will be used to integrate phosphate to ADP producing ATP, and that's how ATP is getting produced in the matrix of mitochondria.

a- how many protons should be pass through ATPase to produce one molecule of ATP? For every 4 protons getting in, there will be one ATP generated.
Therefore, 2 electrons come from NADH, it will produce 2.5 ATP.
(10 protons pumped out/4 protons enter in to produce one ATP)
And FADH2 produces 1.5 ATP→ (6 protons/4 needed).
But scientifically there is no half ATP, that's why they refer that NADH produces 3ATP, and FADH2 produces 2ATP

Uncoupling proteins (back to slide 19)

-what will happen if there is a hole in the mitochondria?

Electrochemical gradient will be affected, accordingly less efficient in ATP synthesis, since we need ATP to build up molecules (anabolism), we cannot build up more fats, carbs, proteins and we will get slimmer! (isn't that good?), as well as the energy dissipated as heat.

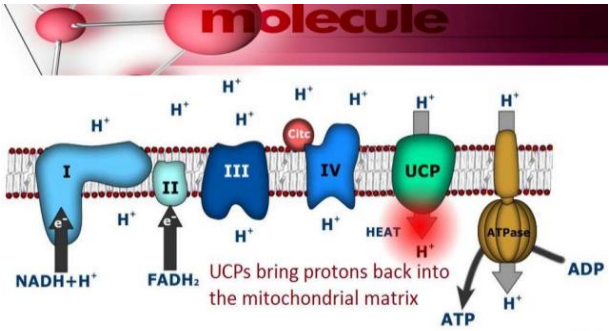
*keep in your mind, that we have two major pathways in the body, either anabolism or catabolism, and sometimes they are shared with each other. Catabolic pathway releases energy, anabolic pathway needs energy.

-can protons move from outside to inside?

No. they need transporters, and there is a lot of holes in inner mitochondrial membrane, through special channels that God creates them, which get back protons from outside to inside, and are called uncoupling proteins. (we studied them in thermogenesis, there is phosphorylation and oxidation-reduction which are coupled with each other, but when we have a 'hole', electrons movement will keep passing, proton pumping will be the same, it won't change, but the phosphorylation will get affected, so both processes won't be coupled, thus we name this hole**: uncoupling protein**.) these uncoupling proteins have so many types, type 1,2,3,4,5…

for example: uncoupling protein 1-called thermogenin, which is exists in brown fats among children more in percentage than other transporter, and brown fats are exists more in children than adults ,which enable them to accommodate the difference in heat content, since they cannot support themselves and get protected from this changes unlike adults.

ATP Content increase -→ getting more obese
ATP Content decrease → getting slimmer



-that's why researchers found that some groups which suffer from obesity have mutation in uncoupling proteins, and they want to invent molecule or drug that get the protons from outside to inside to overcome obesity.

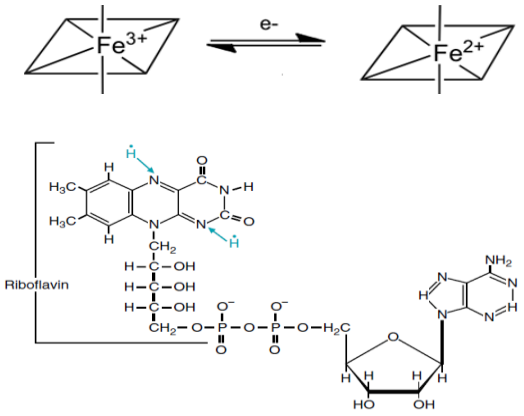
***Types of electron transfer through ETC:**

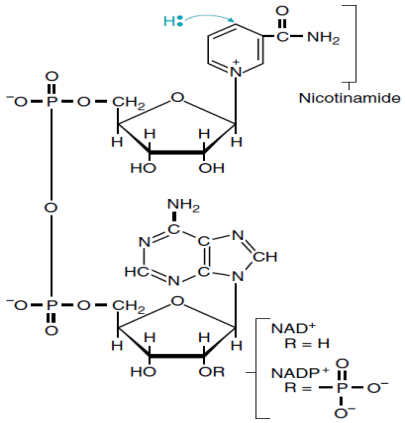
We have 3 types occur in OxPhos:

1 – Direct movement in the form of electrons such as in HEME and METALS, as a reduction of Fe+3 to Fe+2

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

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





***Electron are funneled to a universal electron acceptors**

COENZYME	AS OXIDIZING AGENT	AS REDUCING AGENT
Nicotinamide adenine dinucleotide	NAD^+	$NADH/H^+$
Nicotinamide adenine dinucleotide phosphate	$NADP^+$	$NADPH/H^+$
Flavin adenine dinucleotide	FAD	$FADH_2$
Flavin mononucleotide	FMN	$FMNH_2$

Other electron-carrying molecules "Ubiquinone (some details)"

- Also called coenzyme Q, or Q
- Lipid-soluble benzoquinone with a long isoprenoid side chain
- Small & hydrophobic (freely diffusible)
- Carries electrons through the IMM
- Can accept either 1 e- or 2 e-
- Act at the junction between a 2-electron donor and a 1-electron acceptor
- Sometimes prescribed for recovering MI patients

Ubiquinone (the : (one = ketone group (oxidized) and there are two in the structure, quin= cyclic diene structure (diene= 2 double bonds + 2 oxidized oxygen)

When the first e- comes, one of the keto group becomes OH, and that will be happened for the second keto group, so as a result 2 keto group become reduced.

In addition, we have a long hydrocarbon chain, and repeated 6-10 times..

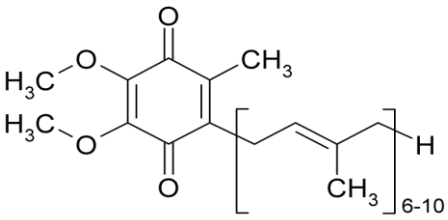
What does that mean?

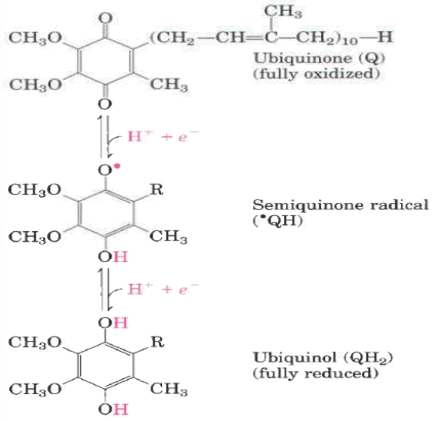
It means that we have a long hydrophobic chains, which allows the molecule to pass through the membrane.

Coenzyme Q is given to patients who are recovering from myocardial infarction (جلطة قلبية).

Myocardial infraction happened when some of the tissues of heart are dead,as a result, the activity will be reduced, and when we give the patient a coenzyme Q, the electron transport will be much faster then ATP generation will be higher.

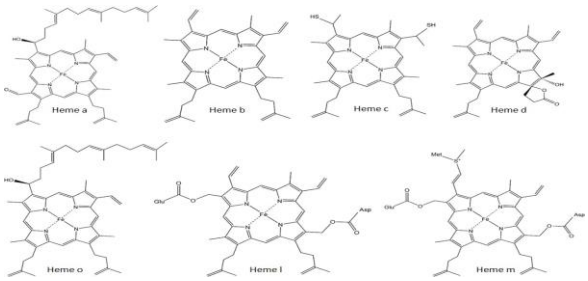
So to overcome the dead tissues (lost of efficiency), increase the no. of working molecules to make more ATP.

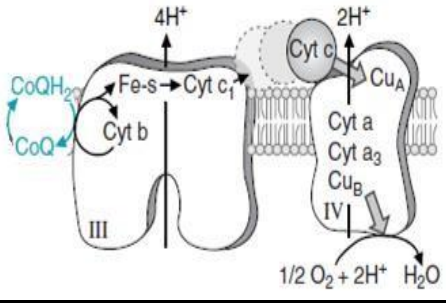




Other electron-carrying molecules “cytochrome”

- **Proteins with characteristic strong absorption of visible light (Fe-containing heme prosthetic groups)**
- **Classification based on light absorption**
- **Mode of binding (a, b, c)**
- **Mitochondria contain three classes o f cytochromes (a , b, & c)**





*Requirement of oxidative phosphorylation:

1- Source and target for electrons(NADH+FADH2 >>O2).

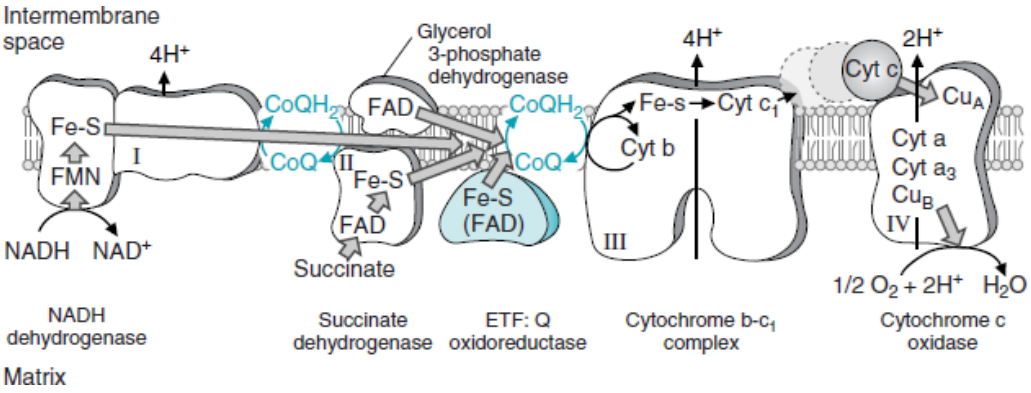
2- Electron carriers.

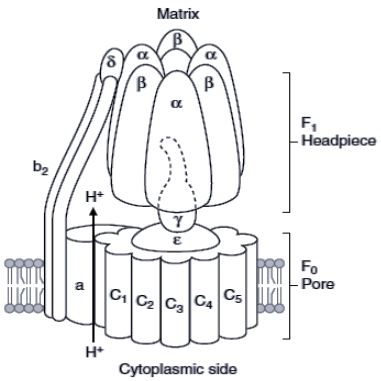
3- Enzymes, like oxidoreductases and ATP Synthase enzymes.

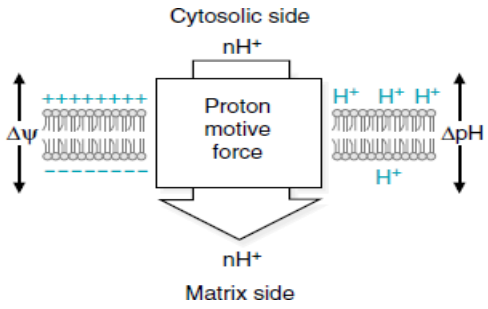
4- Intact inner mitochondrial membrane, because if there is any hole, proton motive force which drive electron transport will be distracted.

*We have studied the first 4 complexes that facilitate ETC (the doctor said that we don't have to go deep through these complexes, it just important to know the carriers – the external components- for each complex to be functional).

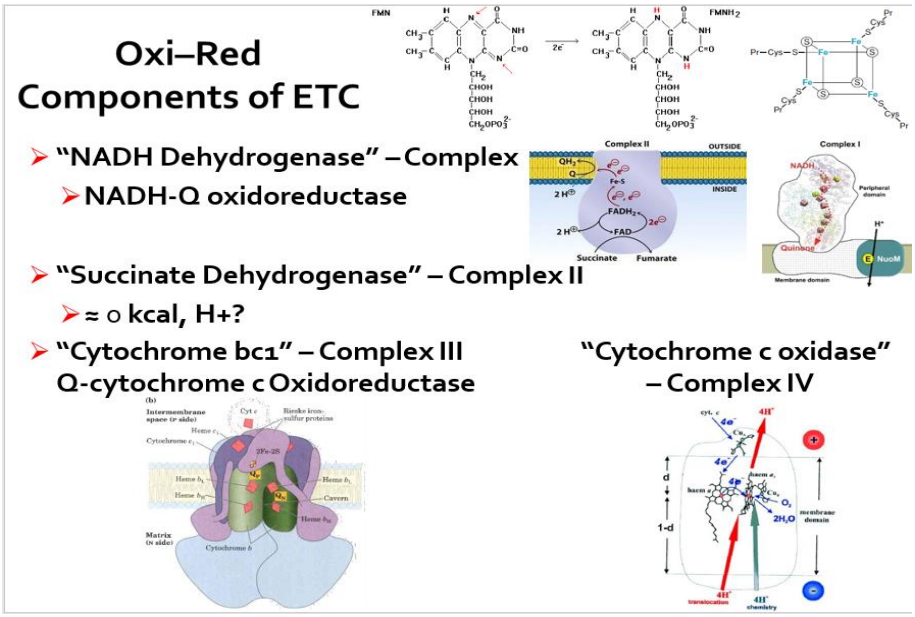
ET to O2, how does the process occurs?
"The chemi-osmotic theory"





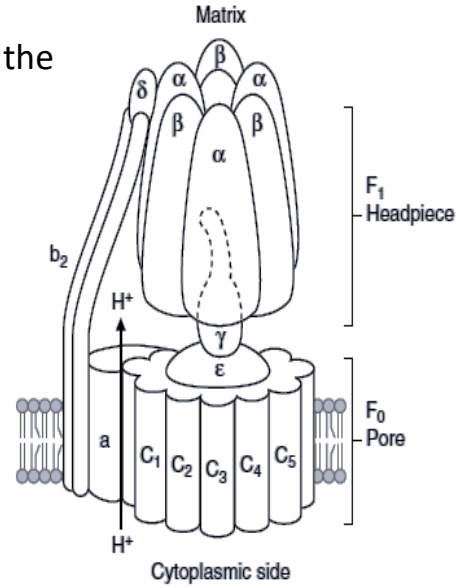


- **Membrane is impermeable to protons (inner membrane so there are specialized carriers and we have discussed that before)**
- **≈ - 16 kcal with each step**



This slide above talked about enzymes and where they exist.

NOW, lets continue talking about the last complex on the ETC which is:



***ATP synthase**

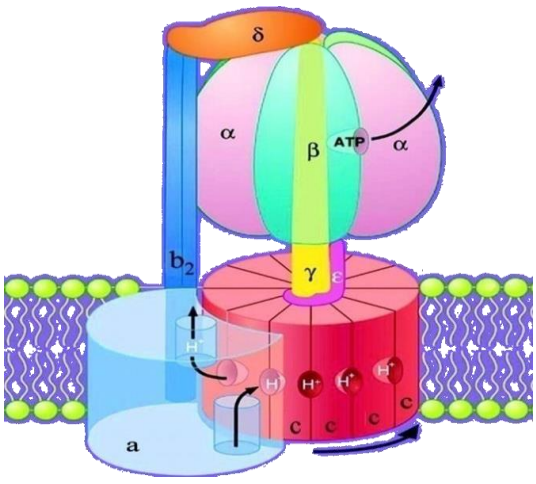
These points will be discussed in a while.

F1:

- **"γ" subunit: rotates**
- **"β" subunit: binds**
- **"α" subunit: structural**
- **3 conformations: tight (T), loose (L), open (O)**

F0:

- **"a" subunit: point of entry & exit**
- **"c" subunit rotates**
- **4H+/ATP**
- **Can run backwards**



As the name implies, it is an enzyme that synthesis ATP, and as any enzyme it can decrease the activation energy and catalyse reactions for both directions (forward & backward), so it also works as ATPase which breaks down the ATP.

*To know how the process goes through this complex, lets know its structure first;

this enzyme consists of **2** portions:

1- **Membrane domain** (within the inner mitochondrial membrane), which is called

F0 Headpiece>> a cylinder rotates in the membrane with 2 parts:

A) Curved shape (C-shape) part that can't move within the membrane, so the cylinder can move around it !, this part called (**a**)subunit which is fixed within the inner membrane and consider as the entry point and exit point for protons.

B) The cylinder which is 12 subunits around each other, each one of them called **c** subunit attached to it **gamma subunit** in the middle that have these properties:

-Its direction toward the mitochondrial matrix.
-Its angled (not straight).
-While **c** subunits moving, it will rotate with the membrane.

2- **Extra membranous domain or Matrix side** (inside th mitochondria) which is called **F1 Headpiece**:

- 6 subunits, ordered in a sequence of alpha>> beta >> etc.
- Its shape like a pyramid.
- 3 Alpha subunits are the **structural subunits** which give the shape for the enzyme.
- 3 Beta subunits are the ones which **catalyse** the conversion of ADP + inorganic phosphate to ATP or vice versa.

NOW! What happen exactly??

- Protons are outside trying to enter according to their motive force and don't have a straight channel to enter through it.
- The only way for the protons to enter is the ATP Synthase, specifically **(a)**subunit.
- They enter through it and directly find one of the **c** subunits (protein) that has in its structure **a glutamic acid** as an amino acid (negatively charged).

- The proton will attach to the Glutamate and it will be protonated >> loss its charge>> conformational change for the protein (which it is a driving force for the rotation occur) >> **c** subunit will move away from the open site>> allow the other proton to come through and attach with other **c** subunit >> conformational change ... etc >> **until full rotation occur**.
- After full rotation: there is another opening in the **(a)** subunit (totally different opening) designed to lose the proton that was attached to it and released to the matrix side.
- This controlled by the difference of PKa and PH values for each area.
- Rotation of **c** subunit induce the angled gamma subunit that attached to it, to hit **B-subunit** (catalytic ones)>> induces conformational change for protein.

  Note: If the gamma subunit is straight, it won't do any action.
- Betta subunit can undergo 3 conformational changes:

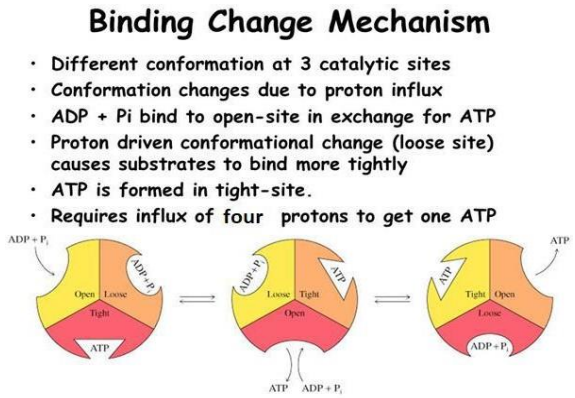
  1) Open 2)loose 3) tight

At first it is open, Open has high affinity for ADP with an in-organic phosphate, when a conformational change is happening, it is turned into loose, which makes ADP and Pi close together, Then another change takes place that makes the subunit tight and generate ATP, and it comes back to open conformation,which has low affinity for ATP, so ATP is released.

ATP synthase can run backward as any enzyme, most enzyme that we studied before, they catalyze forward reactions, so it can act as ATPase depending on electrochemical gradient which is the driving force for ATPase.

When ATP synthase acts as an ATPase? When the electrochemical gradient flipped back → it has to run backward using ATP to generate the electrochemical gradient back.

this process based on the concentration of protons (outside higher than inside). If the concentration of the proton **REVERSED**>> PH will change >> all the process will be reversed>> **catch ATP and releases ADP**.



Check this video, It could be helpful.
https://www.youtube.com/watch?v=IHCzJjm0b1M

*Energy yield… efficiency and efficacy of ETC:

In order to know the efficiency of the ETC, you need to calculate the theoretical yield which is the difference of potential energy between the NADH or FADH 2 and O2.

As you know the capacity of energy for NADH is -53Kcal and -41Kcal for FADH2. On the other hand, the actual yield is 2.5 ATP (-18 kcal) For NADH, and 1.5 ATP for FADH2 (-11 kcal).

- 18/53= 33% efficiency of NADH (low in OxPhos, not as krebs cycle)
- 11/41=26% efficiency of FADH2

The difference in energy goes through (bringing anions from outside to inside and vice versa, Ca+2, generation of heat, Pi and ADP.

- **ΔG°' is so negative, never reversible**
- **Electron transport chain is our major source of heat.**

WE CAN NOTICE THAT ENERGY YIELD IS LOW COMPARED TO CITRIC ACID CYCLE, WHY?

*Energy is lost as heat by uncoupling proteins + energy is needed to bring inorganic phosphate and coupling it with ADP inside mitochondria and take ATP outside it.

*Nothing can cross mitochondrial membrane except by using channels.
*Anything against gradient you have to pay energy for it.
*Delta G is very negative according to the value of reduction potential for electron carriers and enzymes.

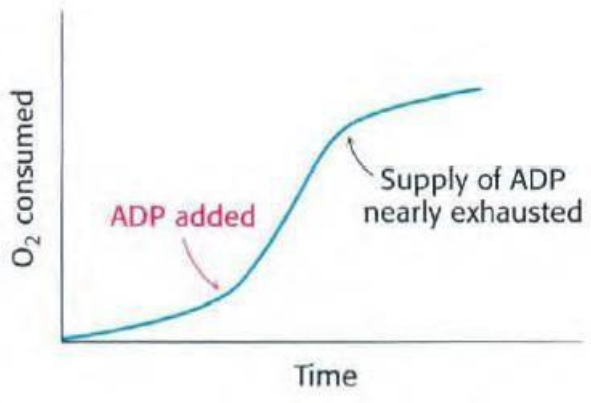
*The ETC is never being a reversible process
*ETC is our major source of heat

*** Regulation for oxidative phosphorylation process is effected by:**

1- **The concentration of ADP**: **the most important factor controlling the process**.

- it's the molecule that control the whole respiratory process >> it's the only allosteric activator for isocitrate dehydrogenase.
-The more O2 is consumed the more efficient and active ETC is.

-The regulation of the rate of oxidative phosphorylation by the ADP level is called **respiratory control**



When you add ADP there's a sharp increase in O_2 consumption and once the ADP supply ends the, rate decreases. This is a physiological way of regulation.

2- Regulation by inhibition:

The mechanism of this regulation is inhibiting the complexes as all of the complexes can be inhibited. (also there is a natural inhibitors for these compounds)

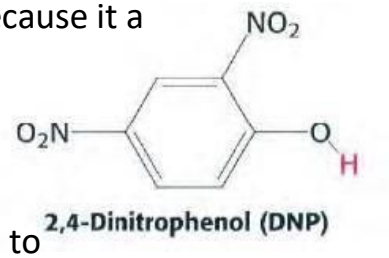
By inhibiting enzymes, we stop the electron transport and the pumping of protons will be stopped. Which will result in decreasing the electrochemical gradient across the membrane. This is fatal because we need high electrochemical gradient for the ATP synthesis process to work effectively.

- Examples of inhibitors:

Specific inhibitor	Target
Rotenone (insecticide)& Amytal(sedative)	**Complex 1 (NADH-Q Oxidoreductase)**
AntimycinA(antibiotic)	**Complex 3 (Q-cytochrome c Oxidoreductase)**
Cyanide (CN-), Azide (N3-), (CO)	**Complex 4 (Cytochrome c oxidase)**
Oligomycin(antibiotic) binds to Fo portion	**ATP Synthase**

- More explanation:

- CO_2 is something different than oxygen, they exchange in the lungs,but in different sites, otherwise metabolically in the body they are so different.
- CO and Cyanide mimic O_2, they go parallel with it, they can bind to where oxygen bind (where you find heme) >> myoglobin/hemoglobin/complex 4 in ETC, so when cyanide for example bind to complex **4** it will inhibit the movement of electrons >>So, no proton will be pumped >> no ATP will be synthesized (because it a coupled process).



2,4-Dinitrophenol (DNP)

3- uncoupling inhibition:

Scientists have worked on producing a chemical that is able to bind with protons and transport
them across inner mitochondrial membrane without producing ATP so it can treat obesity**.**

DNP: 2,4-dinitrophenol is a drug designed with benzene ring structure and hydroxyl group so its lipophilic and can cross the membrane>> then go to mitochondria and cross its membrane >> it can lose and gain its H >> when its on the outer surface of the membrane it picks up H >>when it's toward the matrix it gives its H (because the difference in PH)>> so it picks up the proton from the outside and release it toward the matrix.

- this drug returns the protons back to the matrix >> generating more heat and less ATP>> less anabolism and building up process>> many problems by this chemical inhibitor like: eyes bleeding and blindness and some death cases.

*oxidative phosphorylation diseases:

- **the 5 complexes in ETC are enzymes (proteins),consist of large amount of polypeptides:**

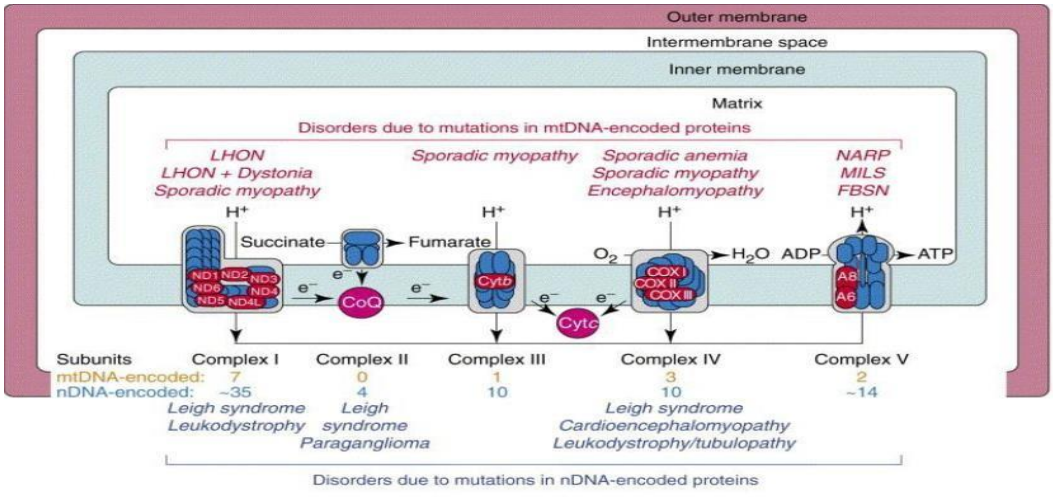
- Mitochondrial DNA works to synthesise part of the complexes polypeptides:

- 7 polypeptides out of 25 for complex1
- 1 subunit from complex 3
- 3 subunits from complex 4
- 2 subunits from F0 portion in ATP Synthase.

- Most of proteins synthesised by nuclear DNA>> translocation to mitochondria.

- So mitochondrial proteins have mixed origin, the mitochondrial DNA make the lowest percentage of them compared to the nuclear DNA.

- The genetic diseases that affect the mitochondria, they might be from mitochondrial origin (from the mother only, it may shows heteroplasmy) or nuclear origin (it will present in all cells of the body).
- inner mitochondrial membrane is filled with proteins so that's why nucleus synthesize higher than 1000 protein.



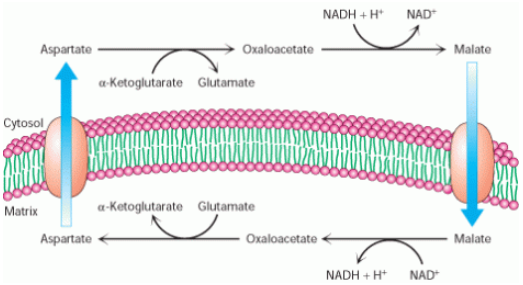
- **Mitocondrial Shuttling Systems**
- **{ Cytosolic NADH }:**

  - Glycolysis is one of the source of NADH from outside the mitochondria

  - There should be a way to get the NADH from outside to inside.
  - it couldn't enter freely, there must be a specific transporter for it, but there is not (why??)>> according to the electrochemical gradient, NADH prefer to exit the matrix of mitochondria toward the intramembranous space by these transporters, and that will affect the process of ETC and ATP Synthesis.
  - so the electrons from the NADH must be used in another form to enter the mitochondria.

NOW , How to translocate the NADH in the cytosol to the mitochondria, to be used as an energy source?

1- Aspartate-Malate shuttle:



-Aspartate can be converted to oxaloacetate by transaminases.

- Oxaloacetate can be converted to malate
- (it's the reversible reaction that found in citric acid cycle , where we form NADH)

but in this REVERSIBLE reaction, cytosolic NADH is used by malate dehydrogenase enzyme >> malate have transporter (because of gluconeogenesis) so it can cross through the membrane>> malate is inside the matrix >> converted to oxaloacete by malate dehydrogenase enzyme and regenerate the NADH so it can go to complex1>> **generate 10 protons**>> **3ATPs**

*note: malate dehydrogenase enzyme has 2 copies:

- **mitochondrial copy** >> convert malate to oxaloacetate.
- **cytosolic copy** >> convert oxaloacetate to malate.

for more clarification:
https://www.youtube.com/watch?v=nEj8b-sg4ps

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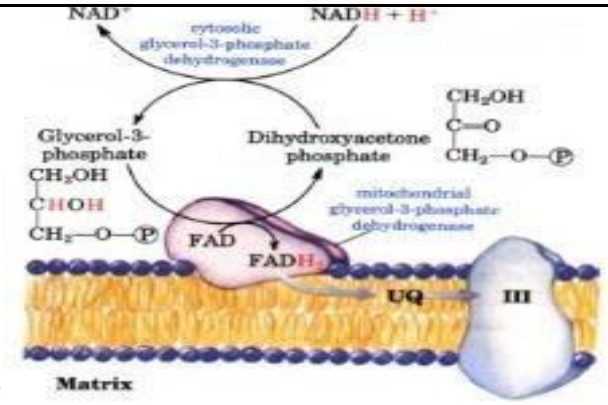

2- glycerol- 3 phosphate shuttle:

- Glycerol 3-phosphate dehydrogenase enzyme:
- Has mitochondrial and cytosolic copie
- This enzyme converts dihydroxyacetone phosphate to glycerol 3-phosphate >> this process (converting ketone to alcohol) uses NADH (take its electrons).
- On the outer surface of the inner membrane, there is the mitochondrial copy of this enzyme that switches the reactions and converts alcohol into ketone extracting the electrons.
- by the coenzyme FADH2 that is found inside the enzyme.
- Generate FADH2 >> coenzyme Q take its electron>>complex 3 (4 proton pumped)>>complex 4 (2 protons pumped) >> **generate 6 protons** >> **2ATP**
- NADH from outside the mitochondria has 2 pathways:

  If it comes through aspartate-malate shuttle it will generate 3 ATPs.

  If it comes through the glycerol-3-phosphate shuttle it will generate 2 ATPs.

  For more clarifications:
  https://www.youtube.com/watch?v=sglxi7I21-M

- ATP –ADP Translocase Enzyme:
  - Also known as adenine nucleotide translocase (ANT), is a transporter protein that enables the exchange of cytosolic ADP and mitochondrialATP across the inner mitochondrialmembrane.
  - Free ADP is transported from the cytoplasm to the mitochondrial matrix, while ATP produced from oxidative phosphorylation is transported from the mitochondrial matrix to the cytoplasm, thus providing the cells with its main energy need.

    This enzyme can undergo conformational changes; inside the mitochondria it has high affinity for ATP, so when it binds to ATP it will Undergo conformational changes and it opens up out, where it

will have low affinity for ATP to release it, and high affinity for ADP to move it inside.

- Notice that; the entry of ADP into the matrix is coupled to the exit of ATP.
- This protein forms 14% of the proteins found on the inner membrane of mitochondria.
- The ratio between ATP and ADP 1:1.
- The Reaction is endergonic; with 25% of energy spent on this enzyme, that's why the efficiency of ATP synthase is not as much as TCA cycle.
- For more clarification: https://www.youtube.com/watch?v=bWATYDuUnLE

good luck and sorry for any mistake.

الشيت طويل حبتين، اعذرونا وموفقين