

METABOLISM

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



MID – Lecture 7

Oxidative Phosphorylation (Pt.1)

وَإِن تَتَوَلَّوْا يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ

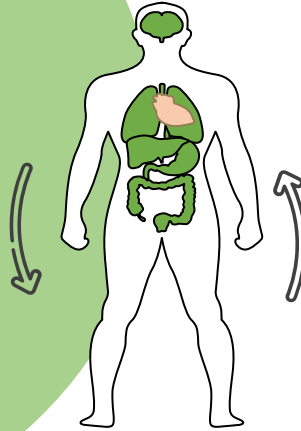
اللهم استعملنا ولا تستبدلنا

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Mitochondria

The mitochondrion has 2 membranes:

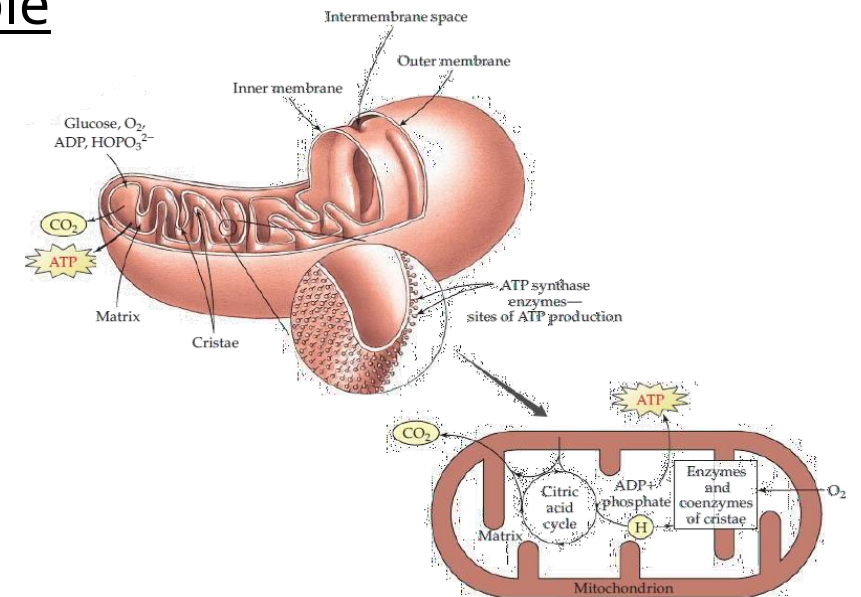
- 1. OMM (outer mitochondrial membrane)** is permeable to:
 - A. Small molecules (MW < 5,000 daltons)
 - B. Ions
 - C. It also has porins (transmembrane channels, **pores**)
- 2. IMM (inner mitochondrial membrane)** is impermeable even to H^+ ; and it has specific transporters.

- IMM bears the components of the respiratory chain and the ATP synthase

We expect a high concentration of proteins in the IMM because it lacks general pores and is composed of about 75% proteins, which include various transport proteins. The outer mitochondrial membrane (OMM), on the other hand, has protein channels and pores typical of other biological membranes.

Remember, the mitochondrion is:

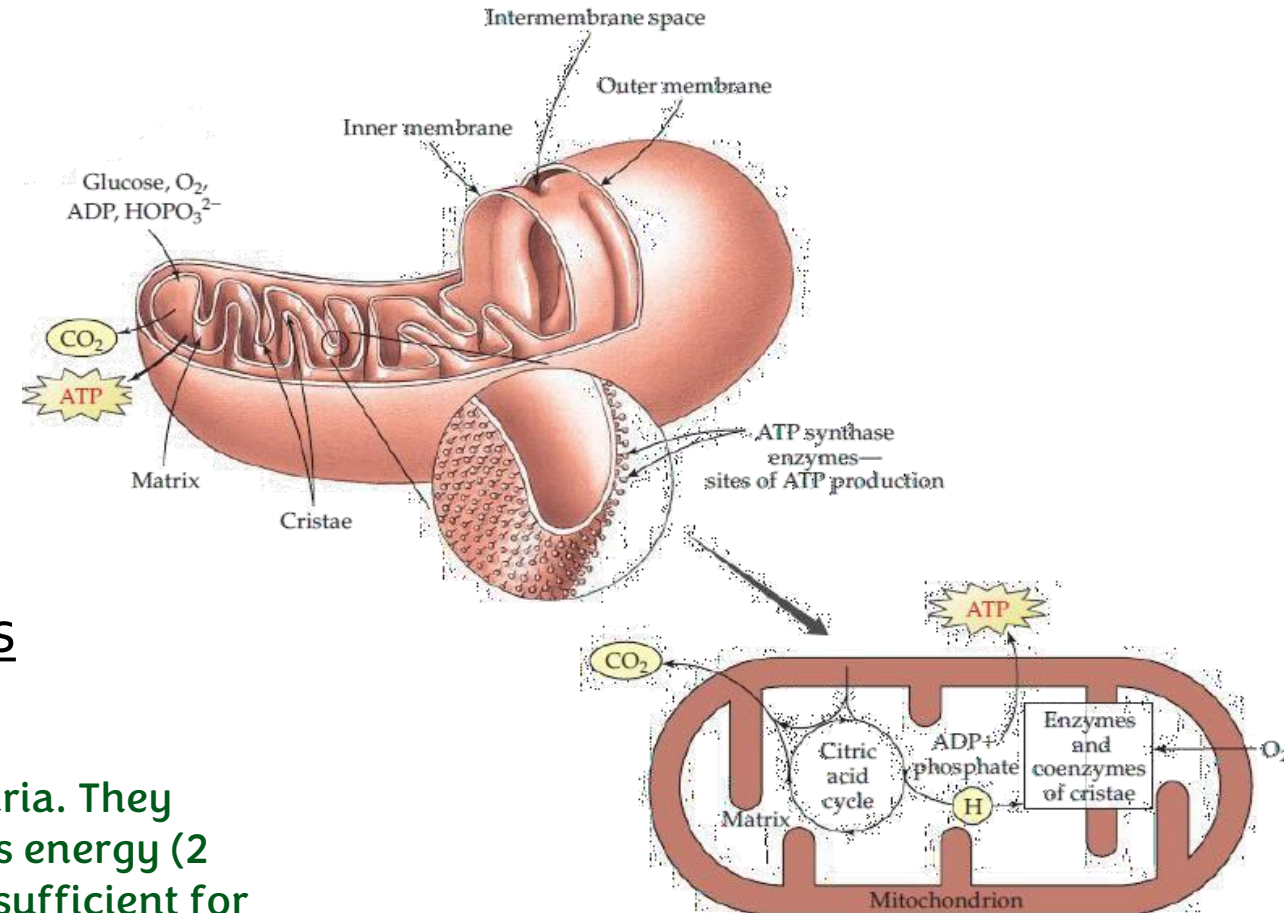
1. A very dynamic organelle
2. The energy factory of cells
3. Present in varying numbers in different cell types depending on the activity of the cell.
4. Capable of dividing and fusing
5. Possesses mitochondrial DNA, RNA & ribosomes



Mitochondria

- **Matrix** (the innermost compartment of the mitochondria): gel-like solution 50% proteins, it contains pyruvate dehydrogenase complex & TCA cycle enzymes, fatty acid β -oxidation pathway, and the pathways of amino acid oxidation. mtDNA, mtRNA, mt-ribosomes
- In other words: matrix contains all pathways of fuel oxidation Except Glycolysis

For example, red blood cells (RBCs) do not have mitochondria. They obtain all their energy from glycolysis, which produces less energy (2 ATP per glucose) compared to aerobic respiration, but it is sufficient for their energy requirements.



Mitochondrial Membranes

- Outer membrane:
 - Similar to cell membrane Around 50% of it is protein
 - 45% cholesterol
 - Less than 3% cardiolipin Bulky phospholipid, with glycerol group

Cardiolipin distinguishes the IMM because of its presence there in a large percentage

- Inner membrane:
 - 22% Cardiolipin
 - No cholesterol
 - Around 75% proteins
 - The remanent (3%) is other lipids.

TABLE 20.3: Location of enzymes in mitochondria

Mitochondria, outer membrane:

Monoamino oxidase

Acyl CoA synthetase

Phospholipase A2

In between outer and inner membrane:

Adenylate kinase

Creatine kinase

Inner membrane, outer surface:

Glycerol-3-phosphate dehydrogenase

Inner membrane, inner surface:

Succinate dehydrogenase

Enzymes of respiratory chain

Soluble matrix:

Enzymes of citric acid cycle

Enzymes of beta oxidation of fatty acid

Mitochondrial Membranes

Proteins that are present in the IMM or OMM are referred to as membrane proteins.

There are also proteins present in the intermembrane space and in the matrix.

Most enzymes that catalyze metabolic reactions are located in the matrix, including enzymes involved in the TCA cycle and β -oxidation (the process of fatty acid oxidation).

Proteins in the IMM, particularly enzymes, may have their catalytic sites oriented either toward the matrix or the intermembrane space, depending on their function.

Glycerol-3-phosphate dehydrogenase, for example, is an enzyme which faces the intermembrane space.

Additionally, succinate dehydrogenase, which functions in the Krebs cycle, faces the matrix because its product, fumarate, remains in the matrix.

Similarly, enzymes involved in the electron transport chain also face the matrix.

TABLE 20.3: Location of enzymes in mitochondria

Mitochondria, outer membrane:

Monoamino oxidase

Acyl CoA synthetase

Phospholipase A2 Degradation of phospholipids

In between outer and inner membrane:

Adenylate kinase NOT adenyl kinase

Creatine kinase Phosphorylate creatine

Inner membrane, outer surface:

Glycerol-3-phosphate dehydrogenase

Inner membrane, inner surface:

Succinate dehydrogenase

Enzymes of respiratory chain

Soluble matrix:

Enzymes of citric acid cycle

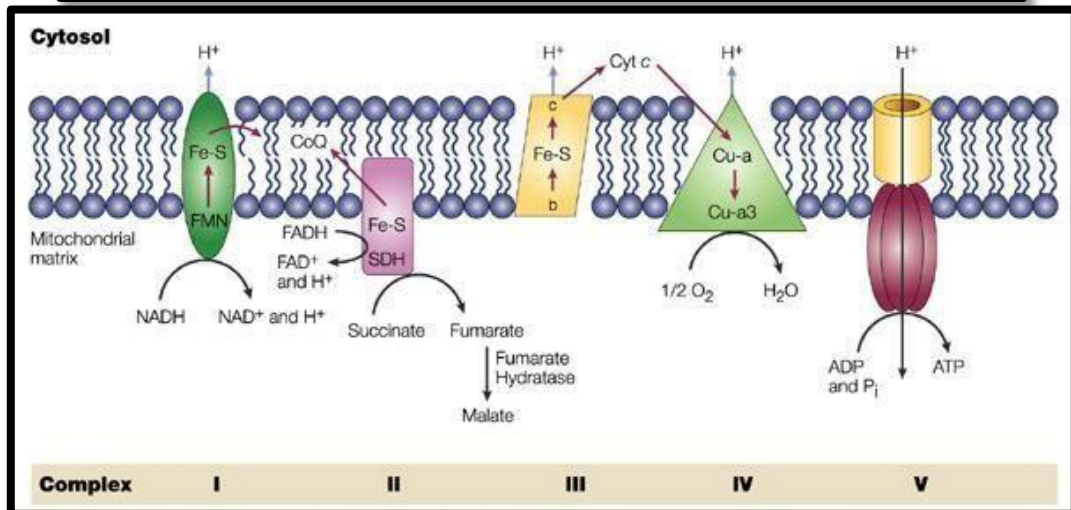
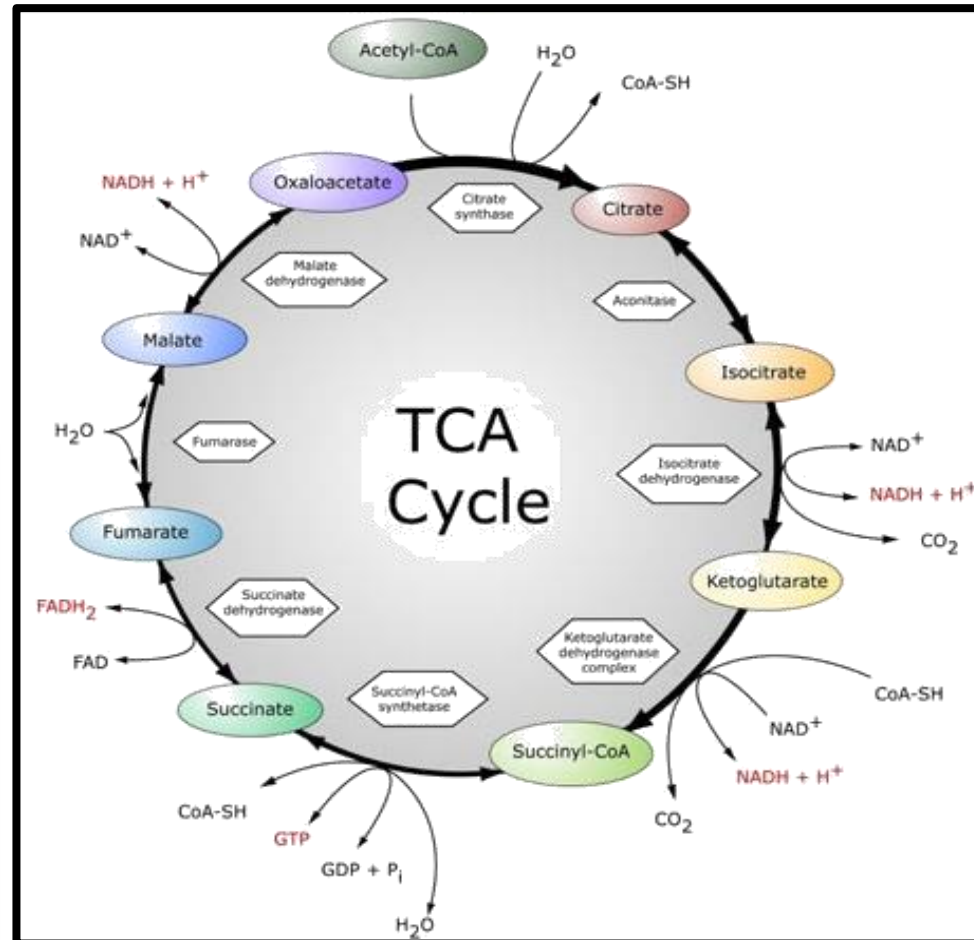
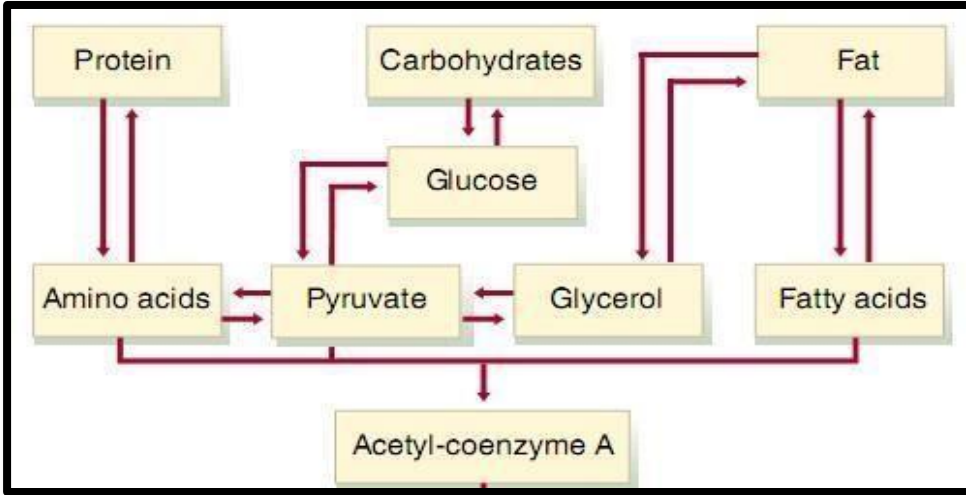
Enzymes of beta oxidation of fatty acid

Where does Oxidative Phosphorylation occur?

- **Stages: Digestion; Acetyl-CoA, TCA, OxPhos**
ETC takes place after Krebs cycle, and after it, Oxidative Phosphorylation (OxPhos) occurs, producing ATP.

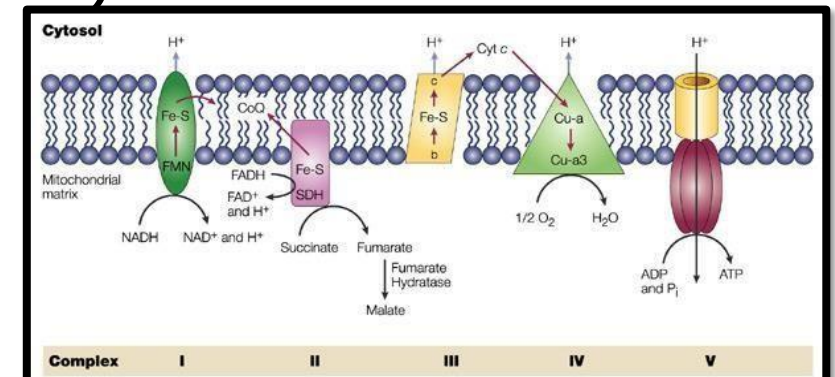
Why is it called oxidative phosphorylation?

1. **Phosphorylation:** Because ADP is phosphorylated to form ATP.
2. **Oxidative:** Because this phosphorylation is driven by a series of redox (oxidation-reduction) reactions that occur in the electron transport chain. This process differs from substrate-level phosphorylation, such as in the conversion of GDP to GTP.



Oxidative Phosphorylation (OxPhos)

- Generation of ATP aided by the reduction of O_2
- Peter Mitchell (1961): the chemiosmotic theory
- Oxidative phosphorylation has 3 major aspects:
 - (1) It involves the flow of electrons through a chain of membrane-bound carriers (prosthetic groups) *This movement of electrons is energetically favorable.*
 - (2) The free energy available (exergonic) is coupled to transport protons across a proton-impermeable membrane *From the matrix to intermembrane space, which creates an electrical gradient (+ out, - in) and a pH gradient (lower out, higher in).*
 - (3) The transmembrane flow of protons down their concentration gradient provides the free energy for synthesis of ATP (ATP synthase)
- Five separate protein complexes I, II, III, IV, and V.
- Complexes I–IV each contain part of the electron transport chain. *Complexes 1-4 are responsible for electron transport while complex 5 is ATP synthase.*
- Each complex accepts or donates electrons to relatively mobile electron carriers, such as coenzyme Q and cytochrome c.

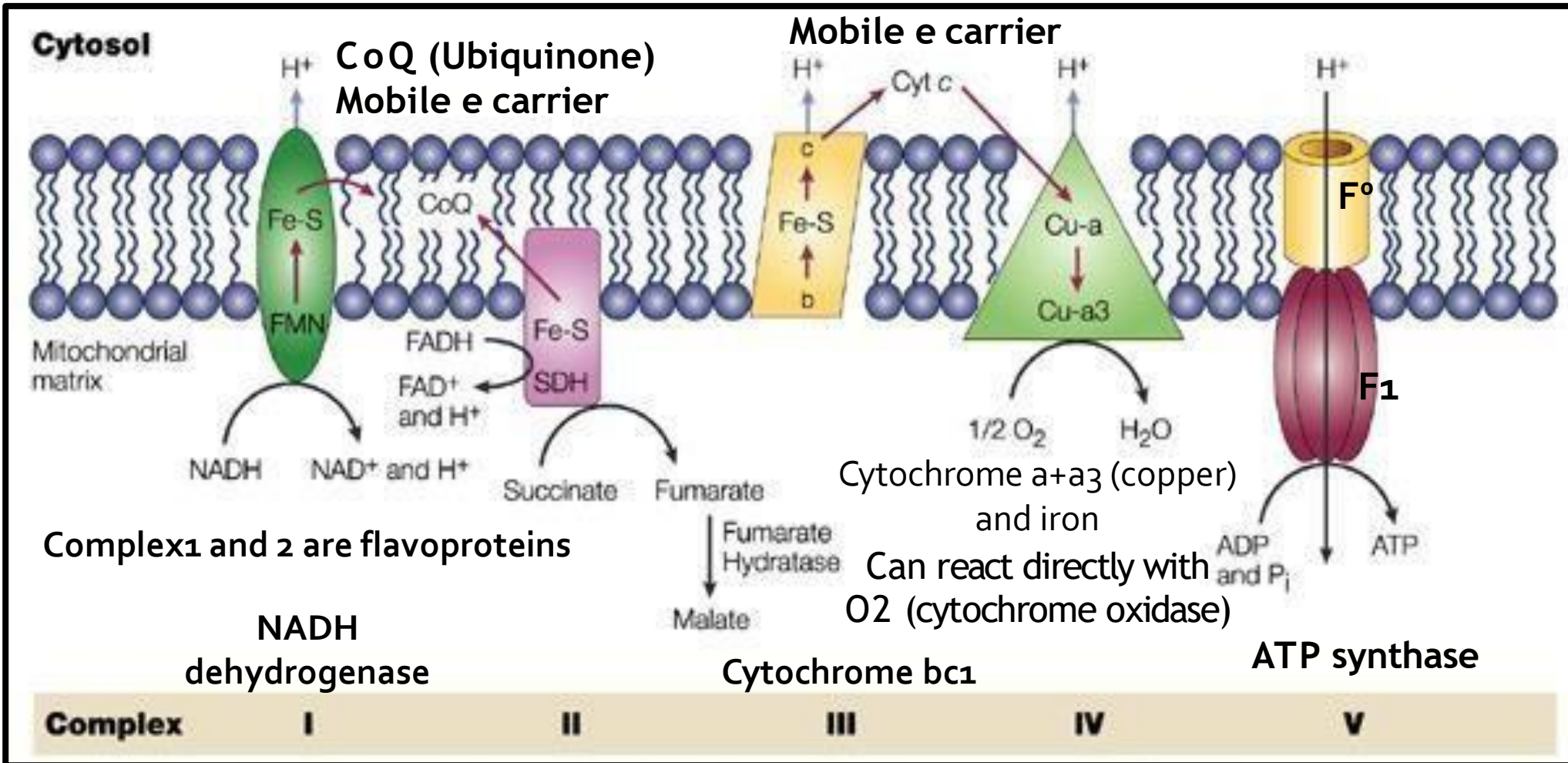


ETC is composed of:

1. proteins (Complexes I-IV)
2. coenzyme Q and cytochrome C (these 2 are mobile)

Oxidative Phosphorylation (OxPhos)

As electrons are passed down the electron transport chain, they lose much of their free energy. Part of this energy can be captured and stored by the production of ATP



NADH: carries electrons in the form of hydride ions (H⁻).

FADH₂: carries electrons in the form of hydrogen atoms (H + e⁻)

Cytochromes:

1. Complex 3 (cytochrome bc₁)
2. Complex 4 (Cytochrome a+a₃)
3. Cytochrome C

Electrons' pathway through Electron transport chain to oxidative phosphorylation:

- Complex I is an enzyme complex (NADH dehydrogenase) that receive electrons from NADH, and it has a tightly bound molecule of (Flavin Mononucleotide), it also contains peptide subunits with Fe-S centers.

In Complex I electrons move this way:

NADH → FMN (becomes FMNH₂) → Fe (in Fe-s) → CoQ

- Complex II is an enzyme complex (**succinate dehydrogenase**, the same enzyme used in the 6th step of the Krebs cycle) that receives electrons from FADH₂. It contains iron-sulfur (Fe-S) clusters.

At Complex II, the electrons move in the following path:

FADH₂ → Fe (in Fe-S centers) → coenzyme Q (CoQ).

- Coenzyme Q (CoQ or ubiquinone), is a mobile carrier and can accept hydrogen atoms both: from FMNH₂, produced on NADH dehydrogenase (Complex I), and from FADH₂, produced on succinate dehydrogenase (Complex II).

FMNH₂ → CoQ → Cytochromes

FADH₂

Note: CoQ, links the flavoproteins to the cytochromes.

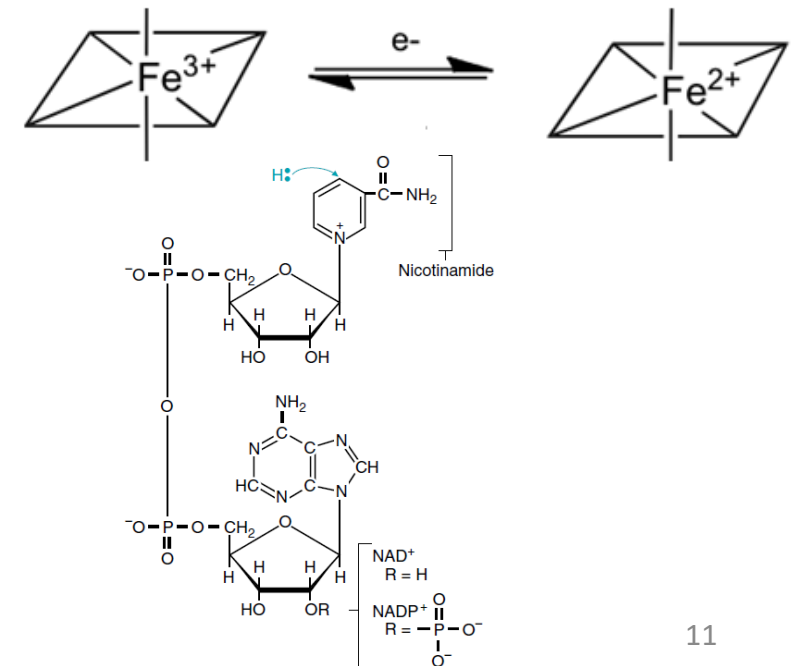
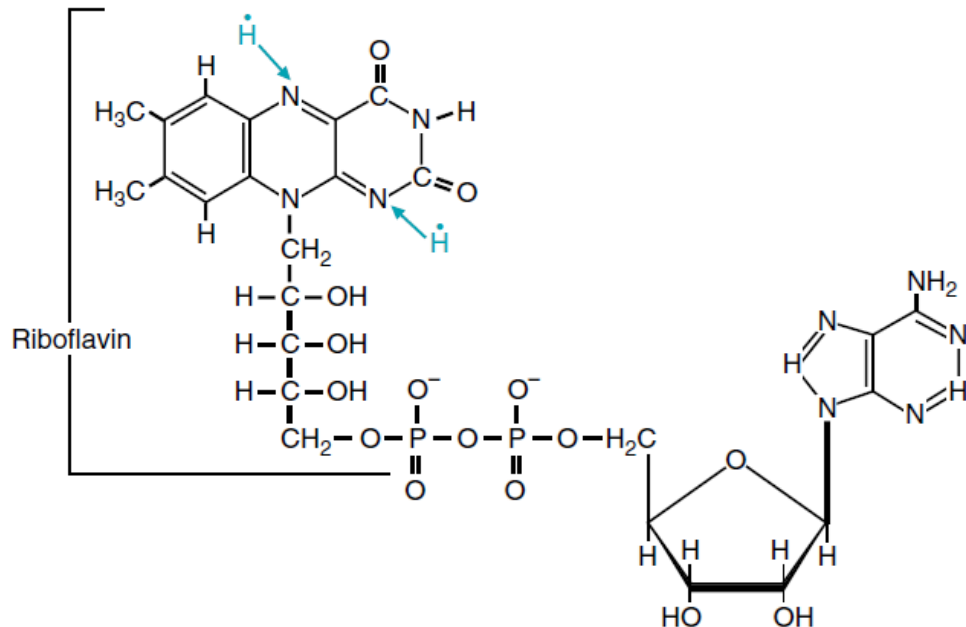
Electrons' pathway through Electron transport chain to oxidative phosphorylation:

- **Cytochromes:** Each contains a heme group (a porphyrin ring plus iron).
Electrons are passed along the chain from:
CoQ → Cytochromes bc_1 (Complex III) → Cytochrome C → Cytochrome a + a_3 (Complex IV)
- **At complex IV** the transported electrons, O₂, and free protons are brought together, and O₂ is reduced to water.
 - This cytochrome complex is the only electron carrier in which the heme iron has an available coordination site that can react directly with O₂, and so also is called **cytochrome oxidase**.
 - **Cytochrome oxidase** contains copper atoms that are required for this complex reaction to occur.
- **The enzyme complex ATP synthase (Complex V)** synthesizes ATP using the energy of the proton gradient generated by the electron transport chain.
 - It contains a membrane domain (F_0) that spans the IMM, and extramembranous domain (F_1) that appears as a sphere that protrudes into the matrix.

Types of electron transfer (ET) through the electron transport chain (ETC)

- **3 types of ET occur in OxPhos:**
 - **Direct ET, as in the reduction of Fe^{3+} to Fe^{2+}** In heme group of hemoproteins
 - **Transfer as a hydrogen atom $\{(\text{H}^+) + (\text{e}^-)\}$** In FADH_2
 - **Transfer as a hydride ion $(:\text{H}^-)$** In NADH

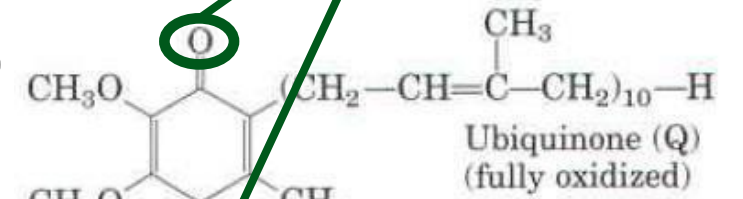
Cytochromes are a specific type of hemoproteins. Unlike hemoglobin where iron remains in the ferrous (Fe^{2+}) state to bind oxygen, cytochromes' iron is reversibly converted between ferrous (Fe^{2+}) and ferric (Fe^{3+}) states. This redox cycling enables cytochromes to carry out their primary function of electron transfer. (slide 12)



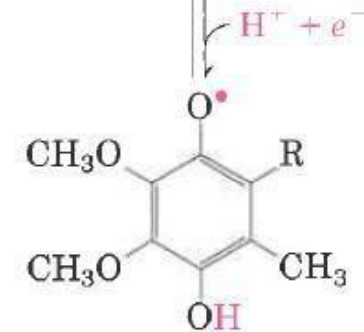
Other electron-carrying molecules

“Ubiquinone”

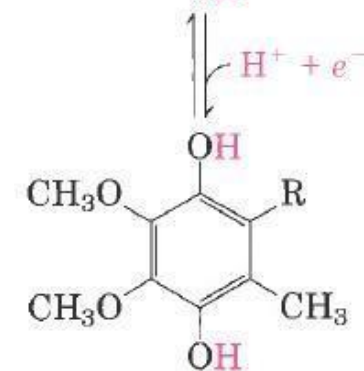
The place where oxidation & reduction happens (ketones)



Ubiquinone is Nonpolar, freely movable, and contributes to different reactions



Semiquinone radical (*QH)



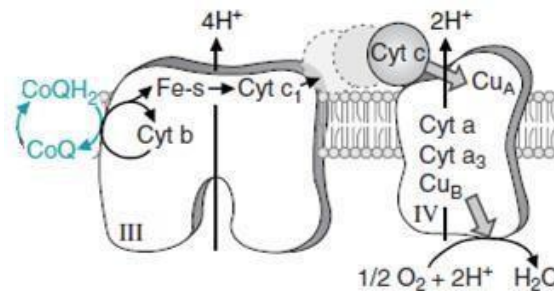
Ubiquinol (QH₂)
(fully reduced)

- Also called coenzyme Q, or Q (ubiquitous in biologic systems)
- 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

Myocardial infarction

Less blood supply -> less nutrients & O₂ to cells -> Ischemia -> cell death. Prescribing CoQ to MI patients enhances ETC.

CoQ enhances mitochondrial energy production, reduces oxidative stress, improves endothelial function, and helps prevent adverse cardiac remodeling, leading to better clinical outcomes.



Other electron-carrying molecules

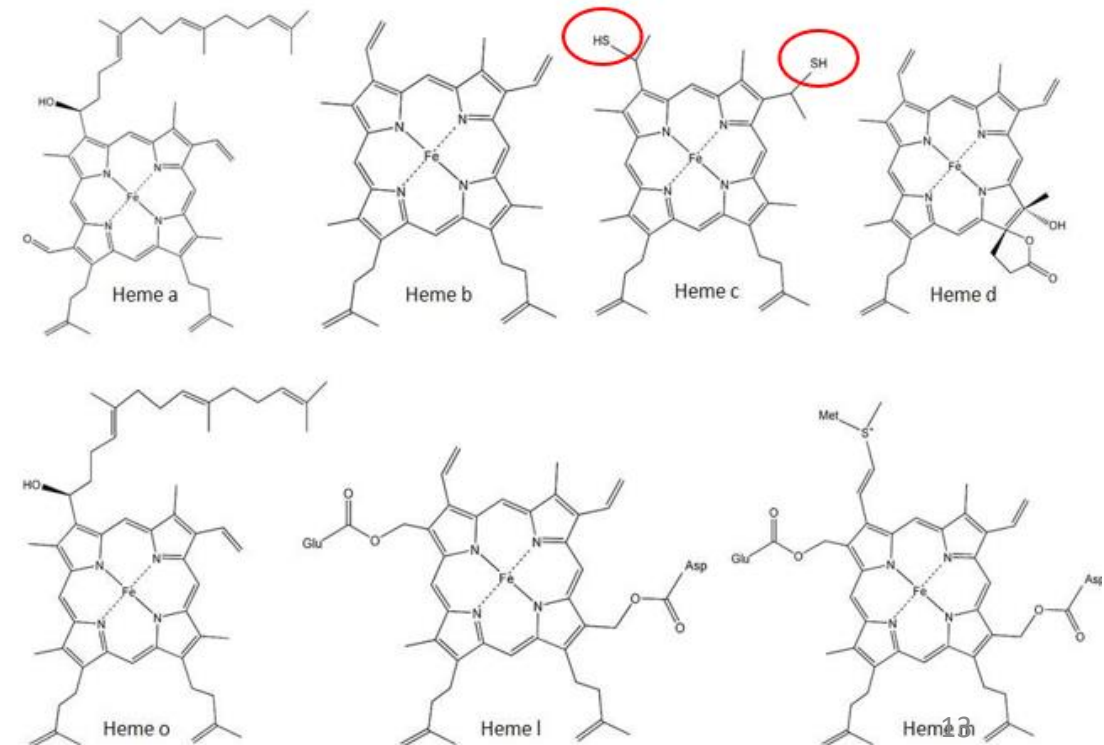
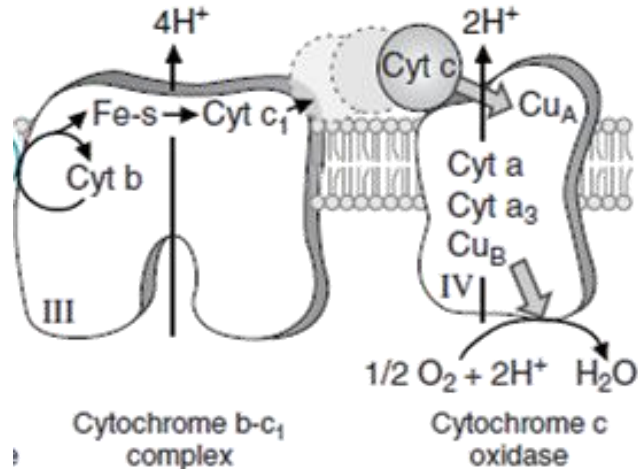
“Cytochromes”

- Proteins with Fe-containing heme prosthetic groups
- Mode of binding (a, b, c)
- Mitochondria contain three classes of cytochromes (a, b & c)

The heme which is a **porphyrin ring (a type of tetrapyrrole) + iron atom in its center.**

The way the heme group binds to proteins can vary, leading to different types of heme.

For example: Heme B is attached to proteins through a single coordination bond between the heme iron and an amino acid sidechain, while Heme C binds to proteins by thioether bonds between cysteine's (SH) groups in it.



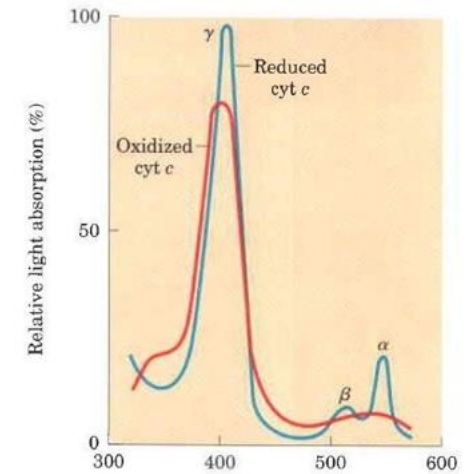
Other electron-carrying molecules

“Cytochromes” Don't worry about numbers, just understand the concept

- Light absorption: Each cytochrome in its reduced (Fe^{+2}) state has 3 absorption bands in the visible range
- α band : near 600 nm in type a; near 560 nm in type b, & near 550 nm in type c
- Some cytochromes are named by the exact α band wavelength:
 - Cytochrome b_{562} ; Cytochrome c_{550} ; Cytochrome c_{551}

- Heme can carry one electron
- $\Delta E^{\circ'}$ depends on the protein Explanation on the right
- Cytochromes a, b & c are transmembrane (c is the exception)

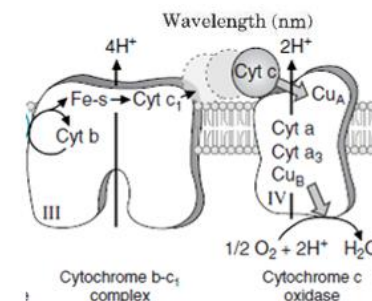
Cyto. c is associated with the outer face of the IMM, and is a mobile carrier of electrons



In the electron transport chain (ETC), the standard reduction potential ($E^{\circ'}$) increases progressively, indicating that each subsequent component has a higher reduction potential than the previous one. This higher $E^{\circ'}$ value allows for efficient electron acceptance as electrons are transferred through the chain.

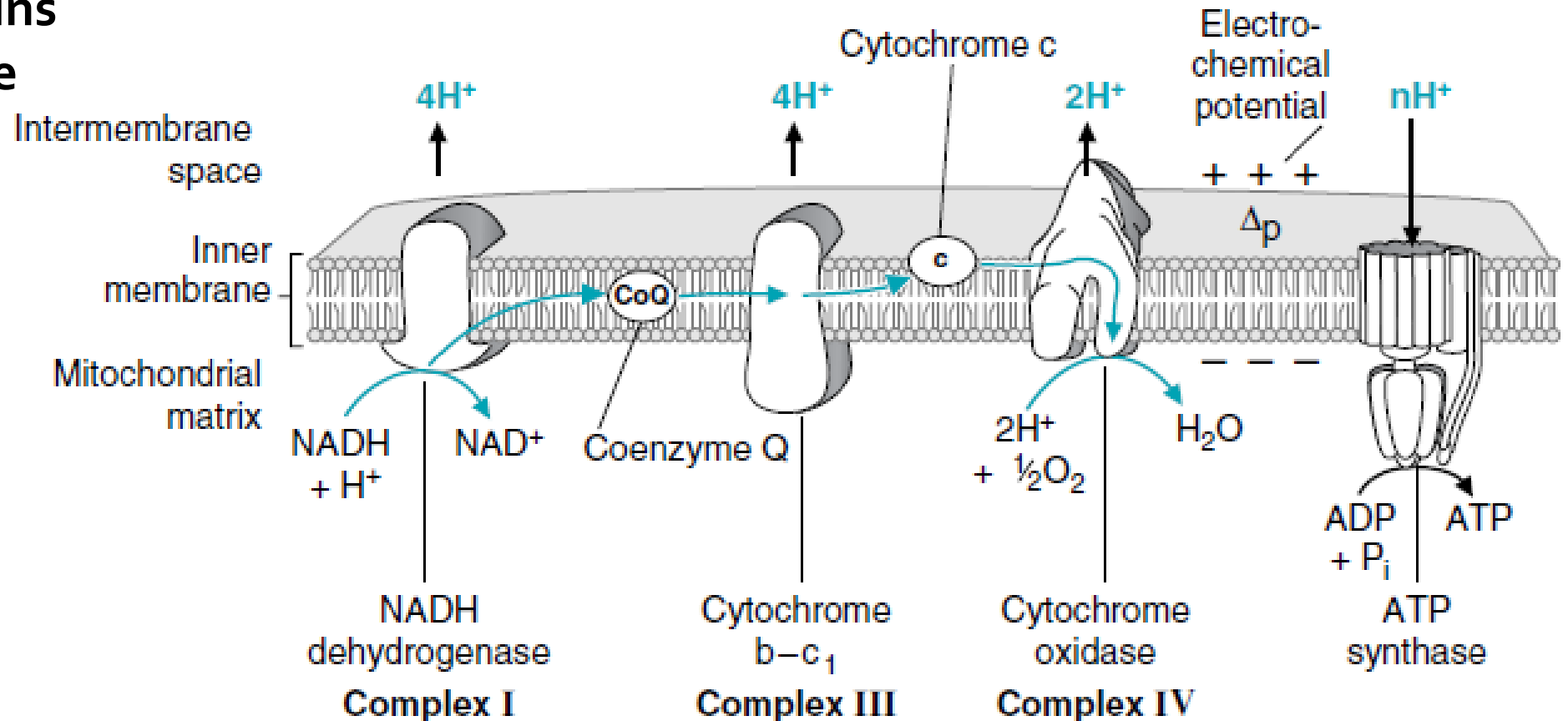
The endergonic process of ATP synthesis relies on these favorable reactions, where the flow of electrons to components with increasingly positive $E^{\circ'}$ values creates a gradient essential for maximizing energy yield in cellular respiration.

Take home message: They vary in their light absorption patterns according to their heme type, and their oxidation state (oxidized/reduced).



Requirements of OxPhos

- Redox reaction: electron donor (NADH or FADH₂) & electron acceptor (O₂)
- An intact IMM
- ETC of proteins
- ATP synthase



For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	7	ETC is composed of: 1. proteins (Complexes I-IV) 2. coenzyme Q and cytochrome C (these 2 are mobile non-proteins)	ETC is composed of: 1. proteins (Complexes I-IV) 2. coenzyme Q and cytochrome C (these 2 are mobile) Cytochrome C is indeed a protein
V1 → V2	4; bottom left 14; bottom right	The remanent (13%) is lipid. The exergonic process of ATP synthesis relies on these favorable reactions,	The remanent (3%) is other lipids. The endergonic process of ATP synthesis relies on these favorable reactions,

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

(numbered in order as cited in the text)

1. Lippincott's illustrated reviews:
Biochemistry 8th edition (Pg 81-84)

Extra References for the Reader to Use:

1. If interested in CoQ for MI patients:
[Coenzyme Q10 for Patients With Cardiovascular Disease: JACC Focus Seminar](#)

يا من يُرَجِّي للشدائدِ كلها
يا من إليه المشتكى والمفرغُ
نرجوك ربنا أن تفرج كربنا وتزيح همنا وتزيل غمنا
بنصرة أخوتنا يا قوي يا متين، وصل اللهم وبارك
على سيد خلقك وحبيبك سيدنا محمد وعلى آله
وصحبه وسلم تسليماً كثيراً.

المشغول بالمقارنة، محروم من السكينة.