



الأيض (١)

Metabolism (1)

BCH 340

**Lecture 4: ETC and oxidative
phosphorylation**

Intended learning outcomes (ILOs)

By the end of this lecture, students will be able to:

- Understand the flow of electrons through the electron transport chain.
- Describe the process of oxidative phosphorylation as a final stage of aerobic cellular respiration (where the majority of ATP is generated).
- Identify some inhibitors of the electron transport chain.

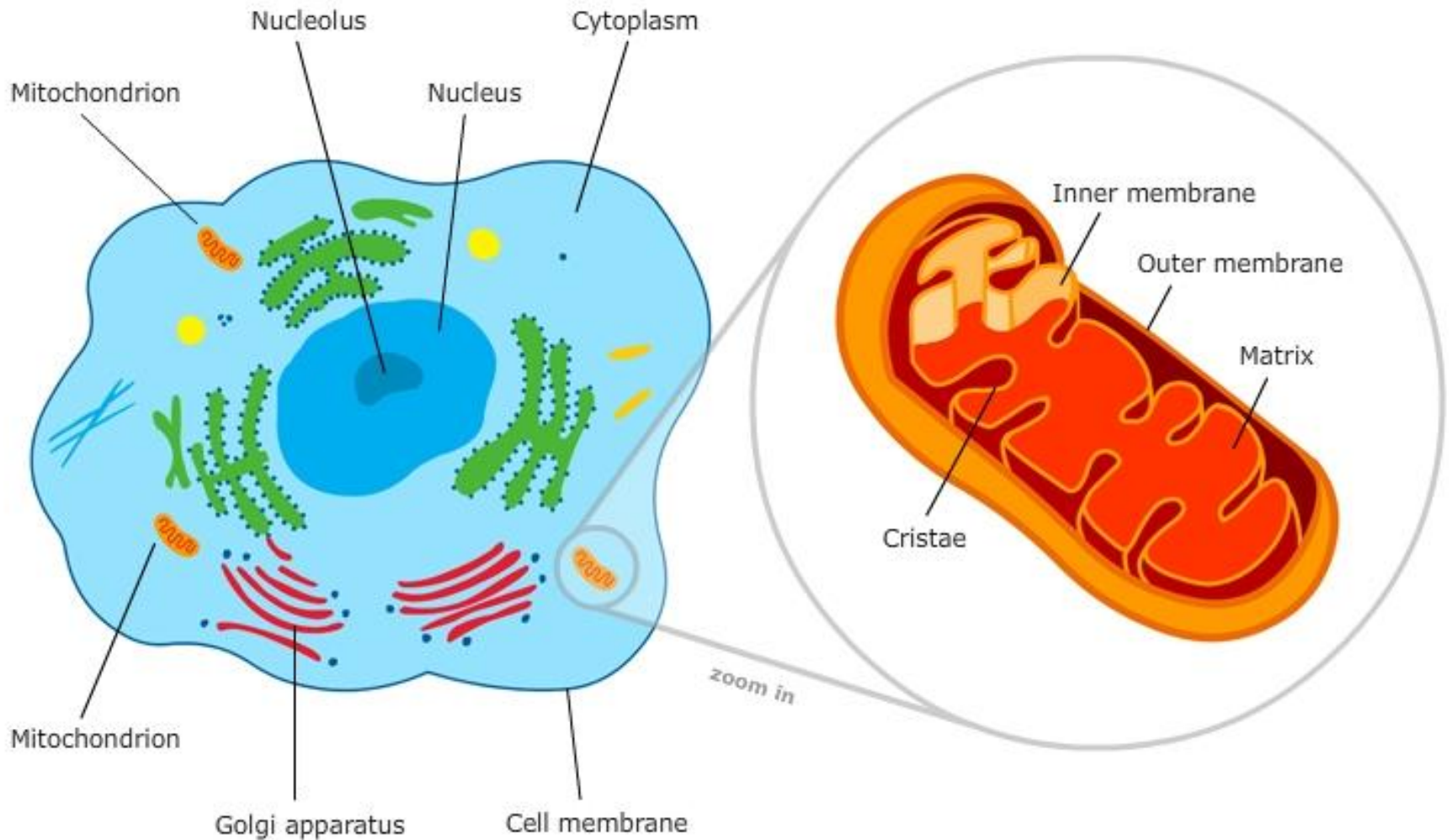
Importance of energy for the cell

- Energy production in cells serves as a fundamental process that sustains life and powers diverse cellular activities, such as:
 - Metabolism (anabolism; biosynthesis of macromolecules)
 - Maintaining cellular homeostasis
 - Cell division and growth
 - Active transport
 - Signal transduction

Cellular respiration

- Cellular respiration is the process through which cells convert biochemical energy from nutrients into ATP (to fuel various cellular activities).
- It's a vital process for all living organisms, as ATP serves as the primary energy source for cells.
- Cellular respiration involves several interconnected metabolic pathways occurring primarily in the cytoplasm and mitochondria of the eukaryotic cells. They include:
 - Glycolysis (in the cytoplasm)
 - Oxidation of pyruvate (in the mitochondrial)
 - Krebs cycle (in the mitochondrial matrix)
 - Electron transport chain (in the inner mitochondrial membrane)
 - Oxidative phosphorylation
 - Anaerobic respiration and fermentation

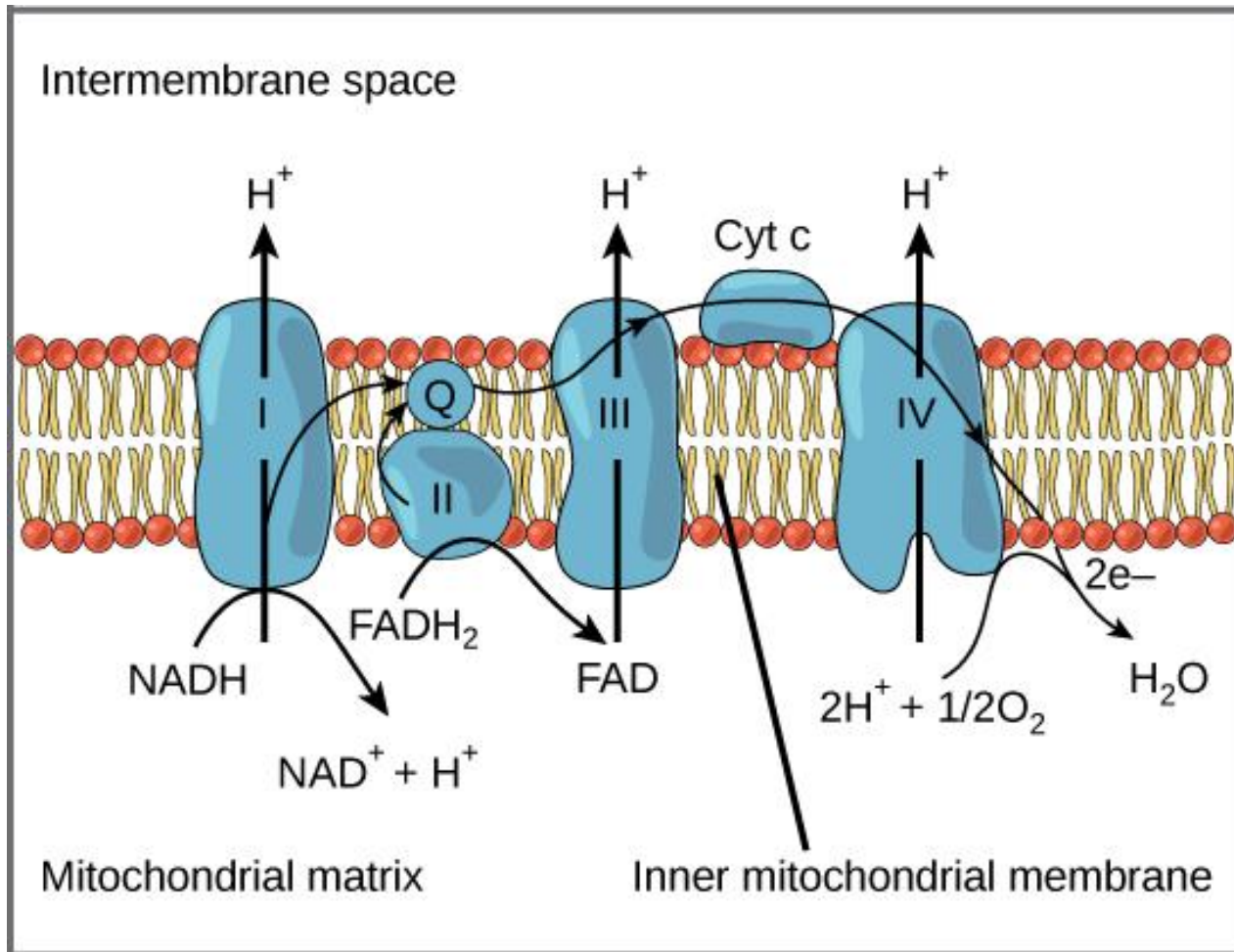
Eukaryotic cell structure



Electron transport chain

- The electron transport chain (ETC) is a critical component of cellular respiration, primarily occurring in **the inner mitochondrial membrane of eukaryotic cells**.
 - In prokaryotic cells, it is found in the plasma membrane
- NADH and FADH₂ generated from glycolysis, pyruvate oxidation, and the Krebs cycle donate electrons to the ETC.
- Electrons move through a series of **protein complexes** (Complex I-IV) and **coenzymes** (Coenzyme Q and Cytochrome c), releasing energy.
- This energy is **used to pump protons (H⁺)** across the inner mitochondrial membrane, establishing an electrochemical gradient.

Electron transport chain (cont.)



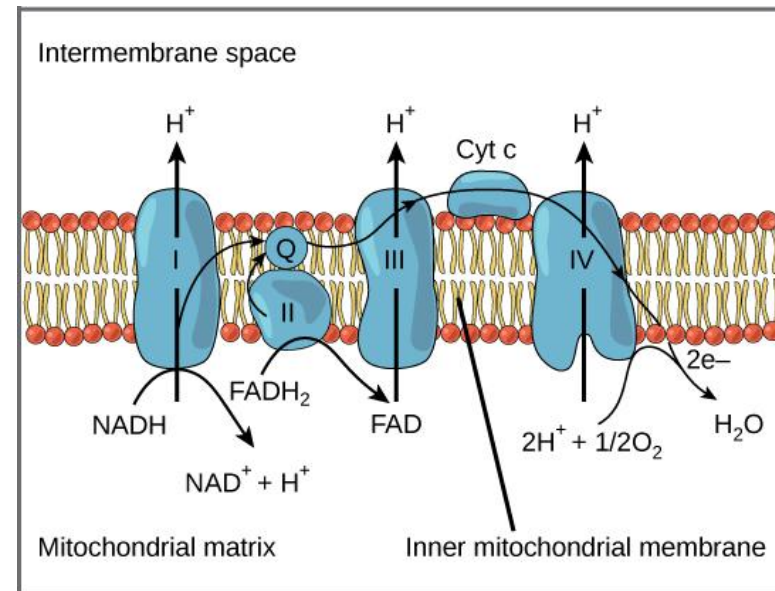
Components of ETC

1. Protein complexes:

The ETC consists of several protein complexes, each containing multiple subunits and cofactors. These complexes facilitate the transfer of electrons along the chain.

Complex I (NADH dehydrogenase):

- Accepts electrons from NADH and passes them to ubiquinone (coenzyme Q).
- It **pumps protons (H^+)** from the mitochondrial matrix to the intermembrane space.



Components of ETC (cont.)

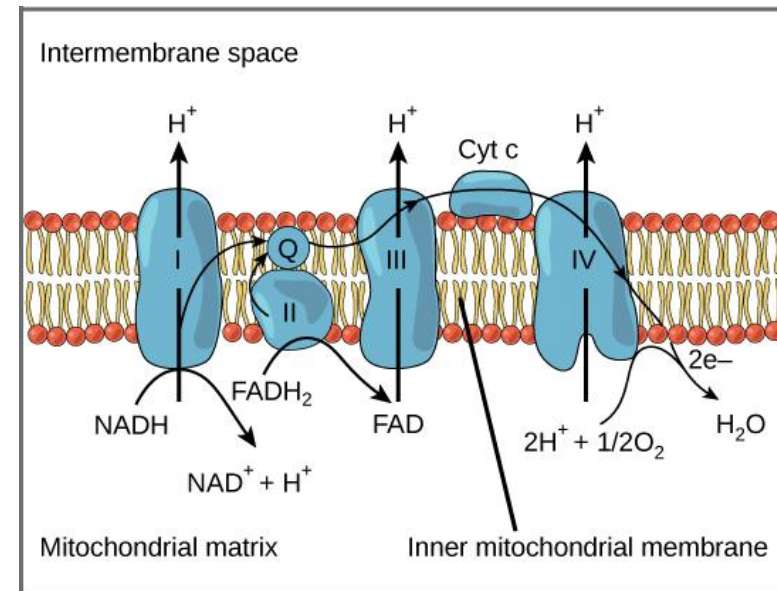
1. Protein complexes (cont.):

Complex II (Succinate dehydrogenase):

- Accepts electrons from FADH_2 produced in the Krebs cycle and passes them to coenzyme Q.
- It is also involved in the Krebs cycle (Step 6) and **does not pump protons**.

Complex III (Cytochrome bc1 complex):

- Accepts electrons from coenzyme Q and passes them to cytochrome c.
- It **pumps protons** from the mitochondrial matrix to the intermembrane space.

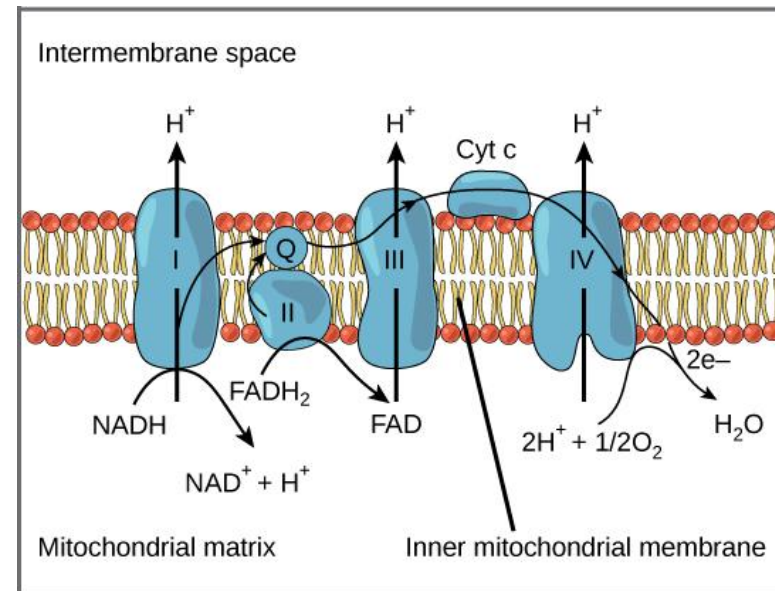


Components of ETC (cont.)

1. Protein complexes (cont.):

Complex IV (Cytochrome c oxidase):

- Accepts electrons from cytochrome c and transfers them to molecular oxygen, forming water as a byproduct.
- It **pumps protons** from the mitochondrial matrix to the intermembrane space.



Components of ETC (cont.)

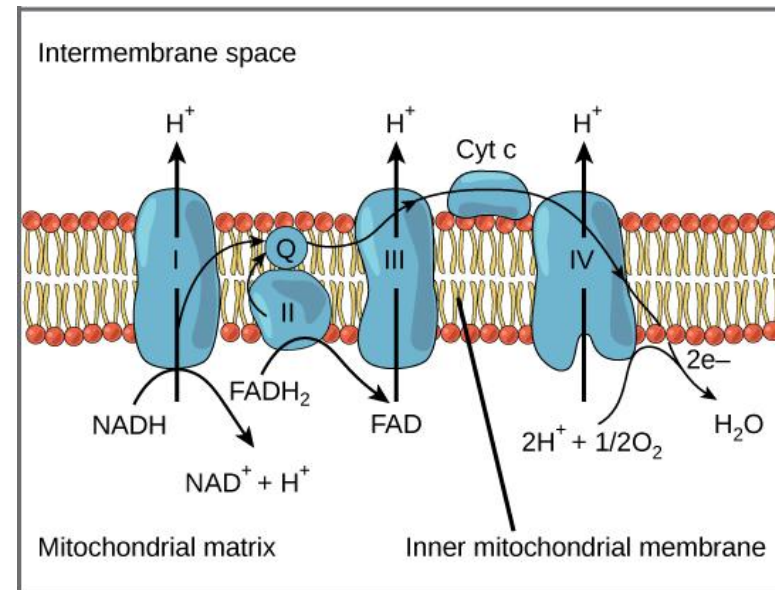
2. Electron carriers

Ubiquinone (Coenzyme Q):

- It acts as a mobile electron carrier between Complexes I/II and III.

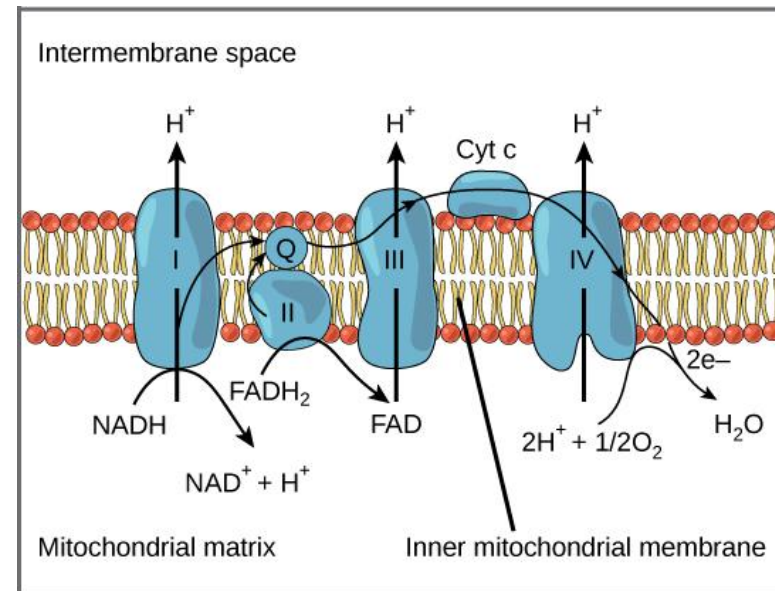
Cytochrome c:

- A small heme protein that shuttles electrons between Complex III and IV.



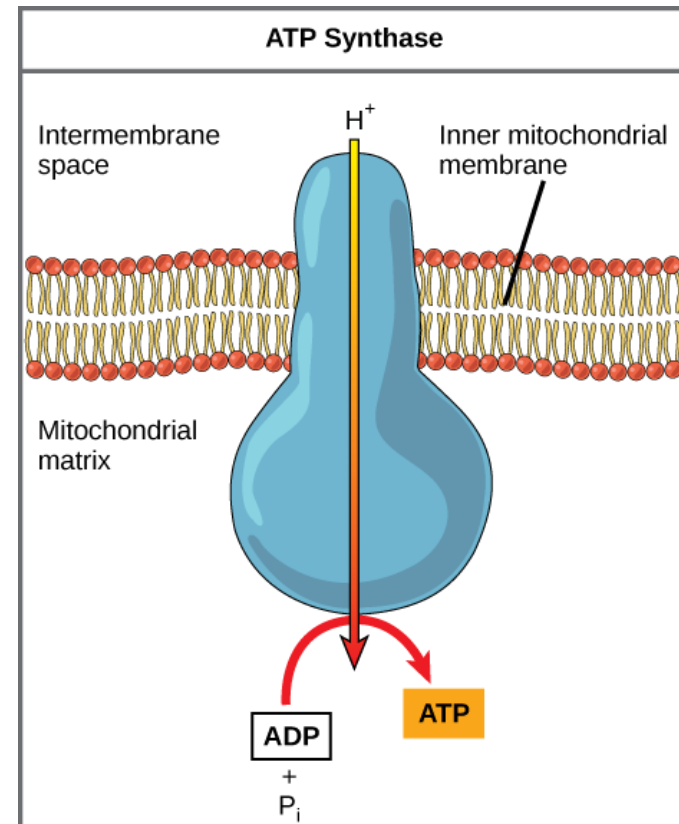
Formation of proton gradient

- Electrons from NADH and FADH₂ are transferred along the ETC, with each complex successively becoming reduced and oxidized.
- As electrons are transferred, energy is released and used to pump protons from the mitochondrial matrix into the intermembrane space, creating a proton gradient (proton motive force).
- Molecular oxygen serves as **the final electron acceptor in the ETC**, accepting electrons from Complex IV and **forming water along with protons**.



Formation of proton gradient (cont.)

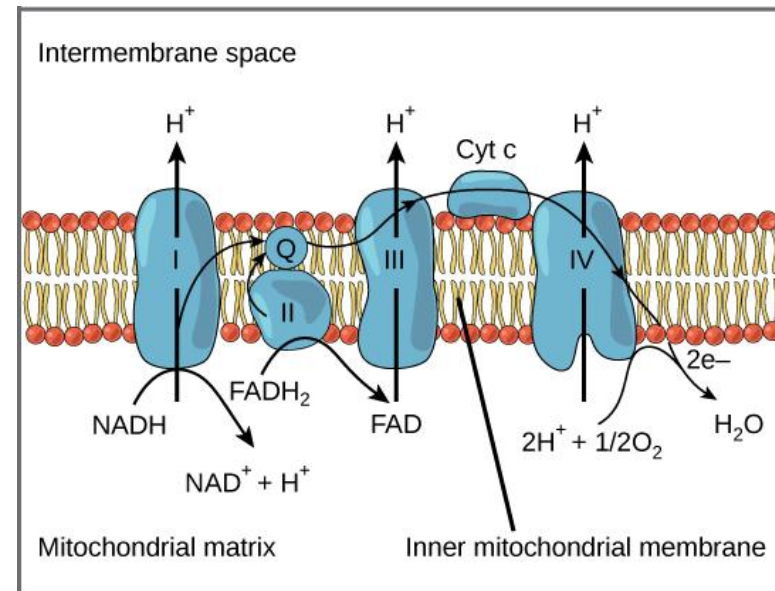
- The proton gradient generated across the inner mitochondrial membrane drives **protons back into the mitochondrial matrix through ATP synthase** (a protein complex embedded in the membrane).
- ATP synthase harnesses the energy of proton flow to catalyze the phosphorylation of ADP to ATP (a process known as **oxidative phosphorylation**).



Role of oxygen in ETC

End of metabolic pathway of ETC:

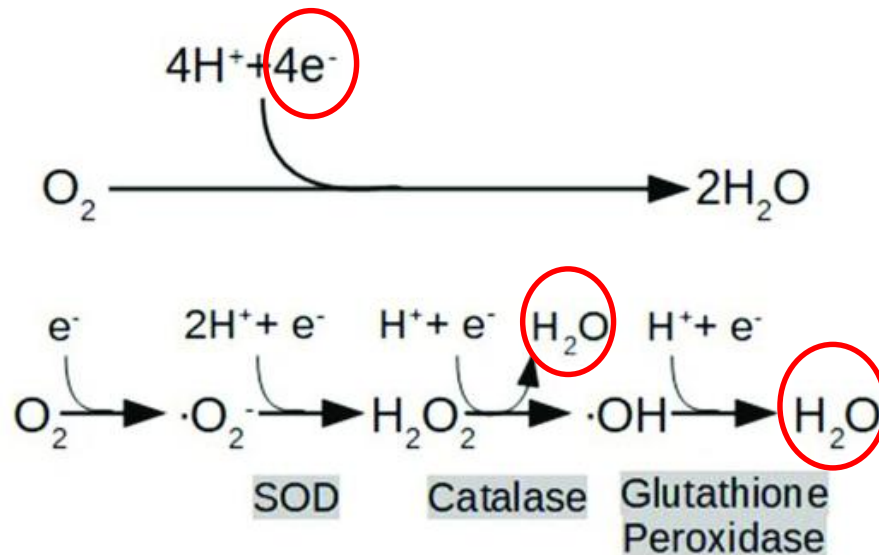
- Oxygen serves as **the final electron acceptor in the ETC** (accepting electrons from Complex IV) **and combining with protons to form water**
- The presence of oxygen ensures the continued flow of electrons through the ETC and the maintenance of the proton gradient necessary for ATP synthesis.
- In the absence of oxygen, electron transport ceases, and ATP synthesis cannot occur efficiently, leading to a decrease in cellular energy production.



Role of oxygen in ETC (cont.)

End of metabolic pathway of ETC (cont.):

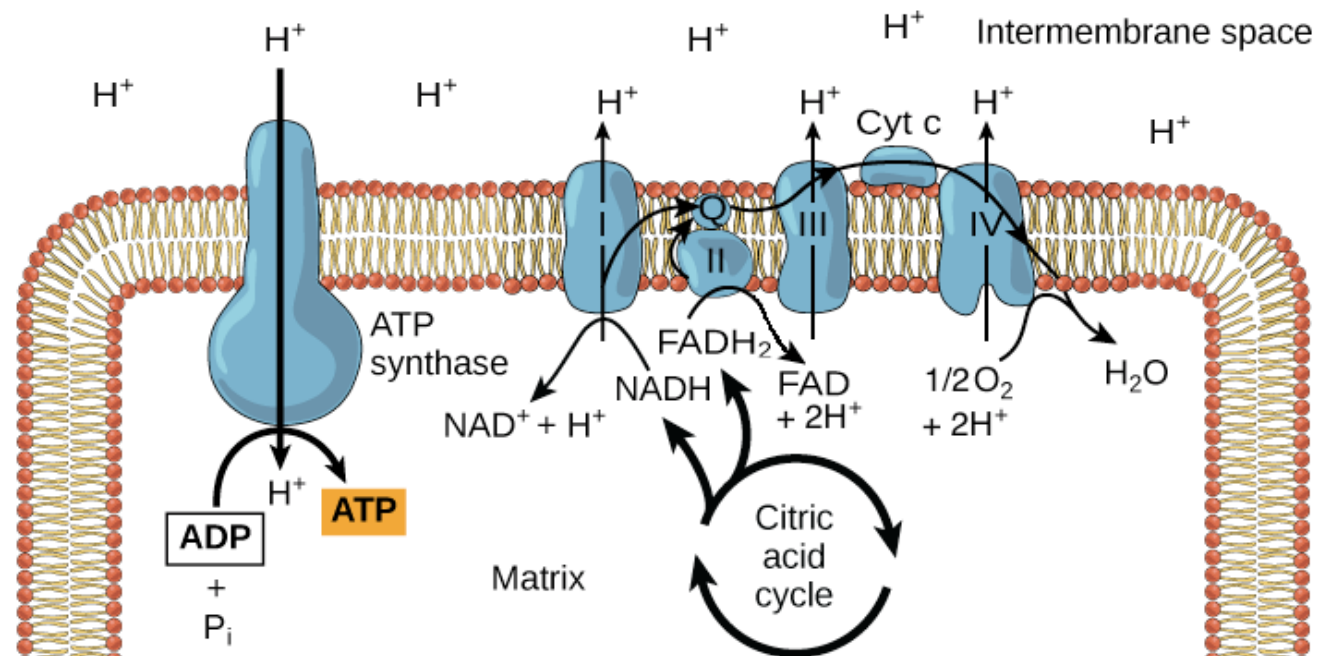
- The reduction of molecular oxygen to water and the formation of reactive oxygen species.



SOD = Superoxide dimutase.

Oxidative phosphorylation

- Oxidative phosphorylation is the final stage of cellular respiration (occurring in the mitochondria of eukaryotic cells) where the majority of ATP is generated.
- It involves the coupling of electron transport through the ETC with the phosphorylation of ADP to form ATP.



Oxidative phosphorylation (cont.)

- During the ETC, electrons from NADH and FADH₂ are transferred through a series of protein complexes, leading to the pumping of protons (H⁺) from the mitochondrial matrix to the intermembrane space.
- This creates a proton gradient across the inner mitochondrial membrane, with a higher concentration of protons in the intermembrane space compared to the mitochondrial matrix.
- The proton gradient established drives protons back into the mitochondrial matrix through a protein complex called **ATP synthase (Complex V)**.

Note:

*The flow of protons across the membrane (proton motive force), coupled with the synthesis of ATP (by ATP synthase) is called **chemiosmosis**.*

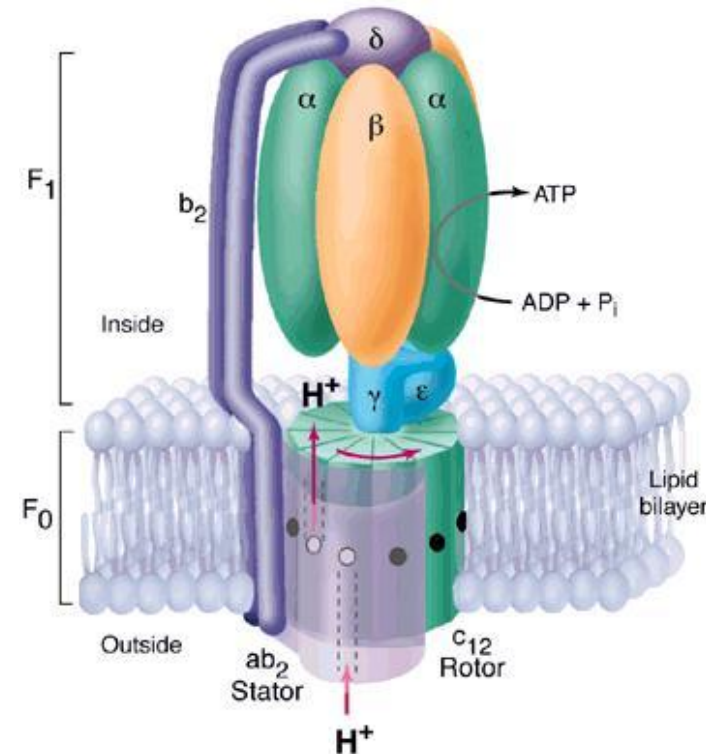
Oxidative phosphorylation (cont.)

ATP synthase:

- ATP synthase acts as a molecular engine, harnessing the flow of protons to catalyze the phosphorylation of ADP to ATP.
- ATP synthase consists of two main components, F_0 and F_1 .

F_0 (water-insoluble integral transmembrane protein):

- It spans the inner mitochondrial membrane and forms a proton channel through which protons flow.
- It consists of multiple subunits vary depending on the organism.

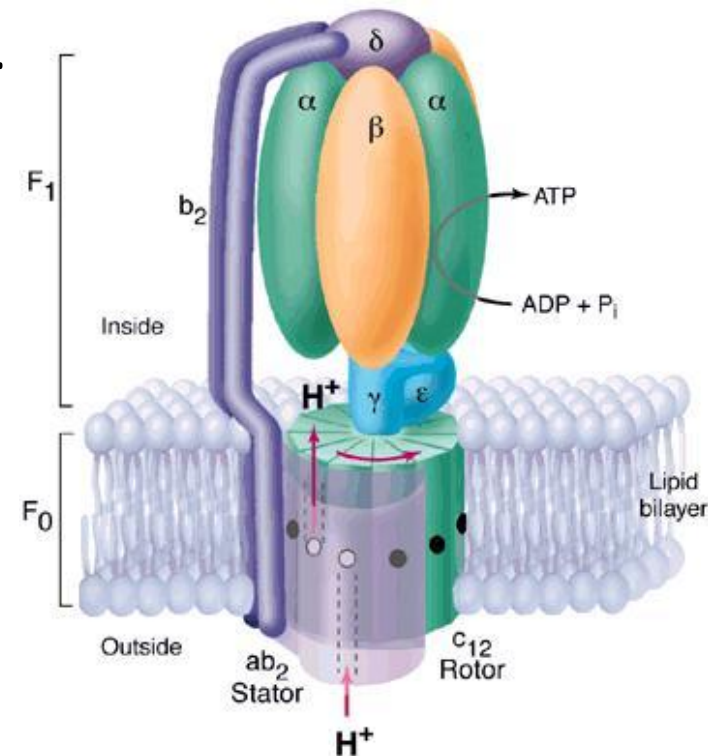


Oxidative phosphorylation (cont.)

ATP synthase (cont.):

F₁ (water-soluble peripheral membrane protein):

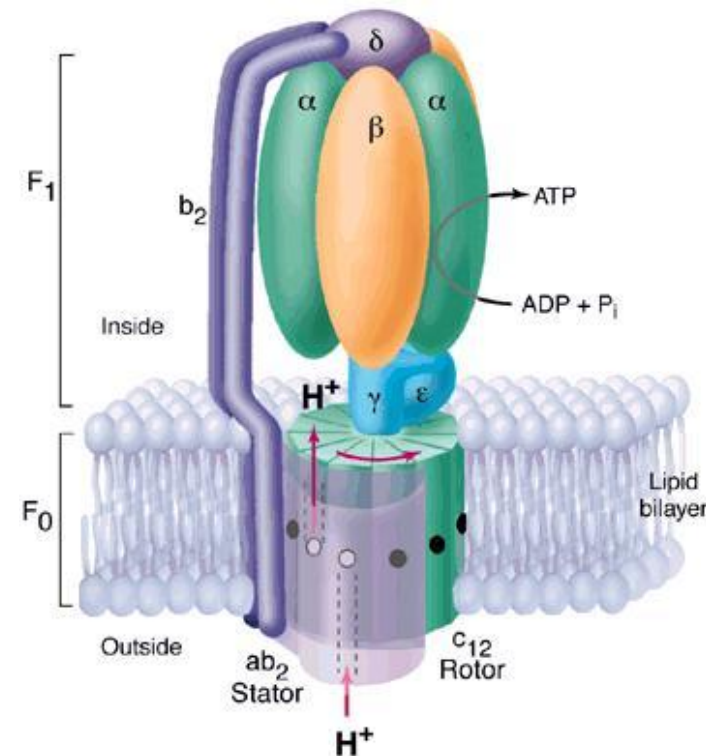
- It is located in the mitochondrial matrix and contains the **catalytic sites** responsible for ATP synthesis.
- It consists of 5 subunits (α , β , γ , δ , and ϵ).
- The peripheral catalytic sites are present on **β subunits**.



Oxidative phosphorylation (cont.)

ATP synthase (cont.):

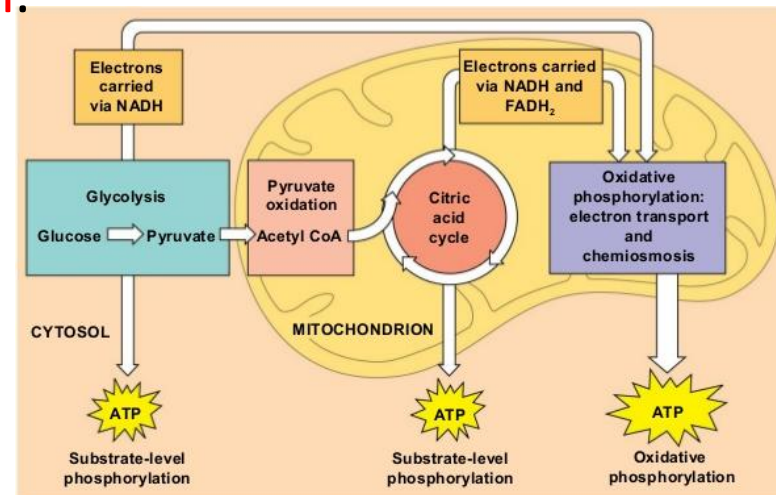
- As protons flow through F_0 (from the intermembrane space back to the mitochondrial matrix) the energy released is used to drive **the rotation of a rotor subunit (γ axel)** within ATP synthase.
- This rotational motion of the rotor causes **conformational changes in F_1** , which promote the synthesis of ATP from ADP and P_i .
- Approximately **one molecule of ATP** is produced by every **three protons pass through** the ATP synthase channel.



Oxidative phosphorylation (cont.)

ATP yield:

- Out of the 38 molecules of ATP generated from the complete oxidation of one molecule of glucose in aerobic conditions:
 - Only 6 ATP molecules are generated from substrate-level phosphorylation (four ATP in glycolysis and two ATP (GTP) in TCA cycle).
 - The majority of ATP molecules (32 ATP) are generated by the ETC and oxidative phosphorylation.



Oxidative phosphorylation (cont.)

ATP yield (cont.):

NADH:

- NADH generated during glycolysis and the Krebs cycle produces ATP through oxidative phosphorylation.
- For each NADH molecule oxidized by the ETC, approximately **3 ATP** molecules are synthesized.

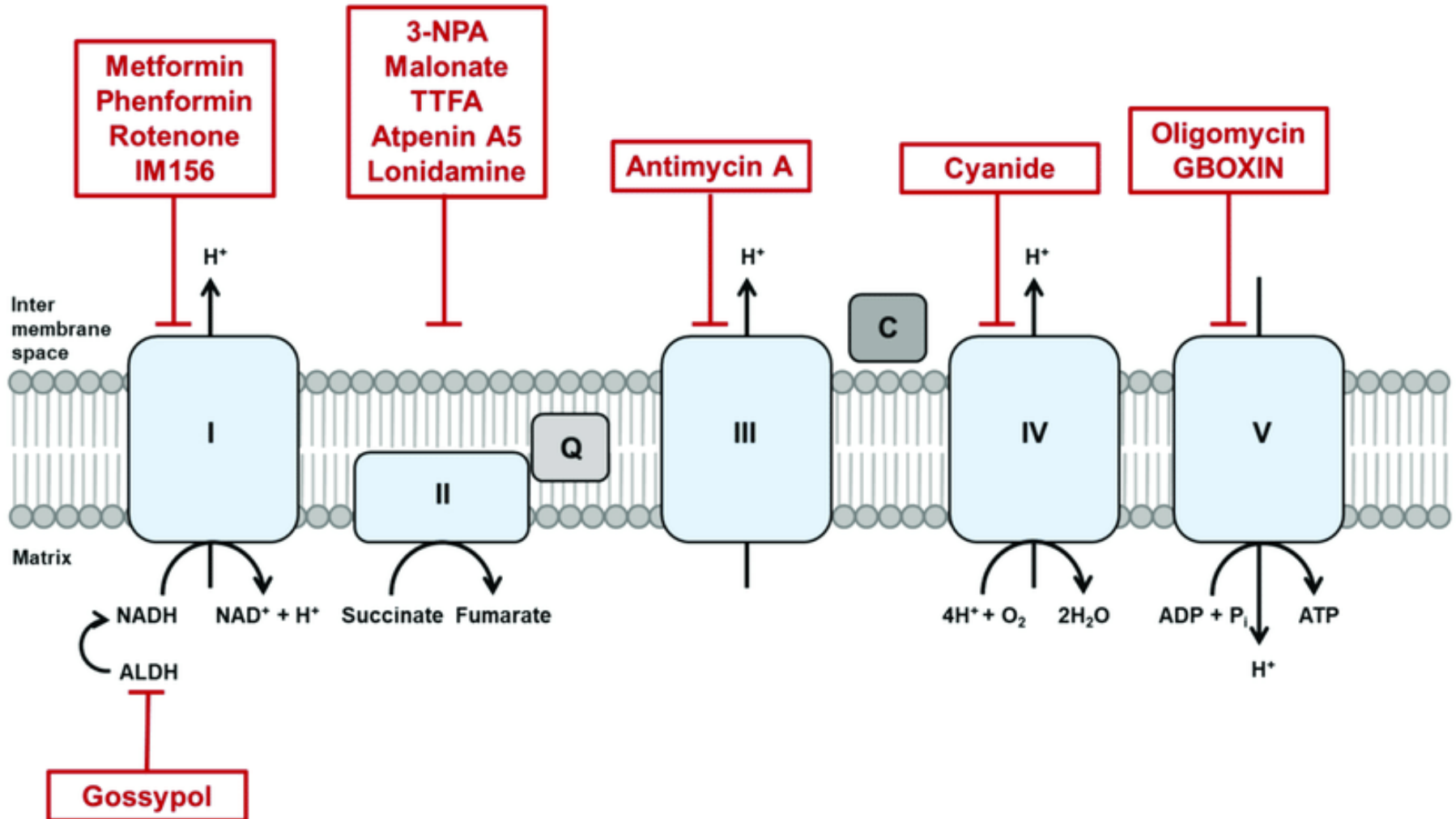
FADH₂:

- FADH₂ generated specifically in the Krebs cycle also contributes to ATP production.
- Each FADH₂ molecule oxidized by the ETC produces approximately **2 ATP** molecules.

Inhibition of respiratory chain

- Inhibition of the respiratory chain is the process by which the activity of one or more components of the ETC is impaired, leading to a decrease in the flow of electrons and ultimately affecting ATP synthesis (energy production).
- Several factors and substances can inhibit the respiratory chain, disrupting cellular energy metabolism. Some examples include:
 - **Rotenone:** inhibits Complex I (NADH dehydrogenase).
 - **Malonate:** inhibits Complex II (succinate dehydrogenase).
 - **Antimycin A:** inhibits Complex III (cytochrome bc1 complex).
 - **Cyanide and carbon monoxide:** both inhibit Complex IV (cytochrome c oxidase).
 - **Oligomycin:** inhibits Complex V (ATP synthase).

Inhibition of respiratory chain



Summary

- The ETC plays a crucial role in ATP production during cellular respiration.
- It efficiently converts the energy stored in NADH and FADH₂ into ATP through the generation of a proton gradient and subsequent chemiosmotic synthesis of ATP.
- Oxidative phosphorylation (by the action of ATP synthase) generates a significant portion of the total ATP yield during cellular respiration.
- The ATP yield from oxidative phosphorylation provides cells with the energy required for various metabolic activities and physiological processes.