بسم الله الرحمن الرحيم

RESPIRATORY BLOCK

The Respiratory Chain

إعداد الطالبات

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دعواتكم لنا بالتوفيق في الدارين

The Respiratory Chain

Bio team 429

- Energy is produced by metabolizing energy – rich molecules
  - Ex. Glucose is metabolized by a series of oxidation reaction ⟶ Co_2+H_2o+electrons
- The electrons are donated to specific co enzymes ⟶ NAD^++FAD
- The coenzymes are reduced to energy rich forms ⟶ NADH +$FADH_2$
- NADH and $FADH_2$ donate a pair of electrons to a specialized set of electron carriers called: **Electron transport chain**
- The electrons lose their free energy which is stored with ADP+P_i (inorganic phosphate) to form ATP. HOW?
- Like this: ADP + P_i + energy ⟶ ATP (is oxidative phosphorylation)
- The remainder of the energy not used in ATP formation …..is used to generate heat and Ca^{+2} transport into mitochondria (drive ancillary reactions)

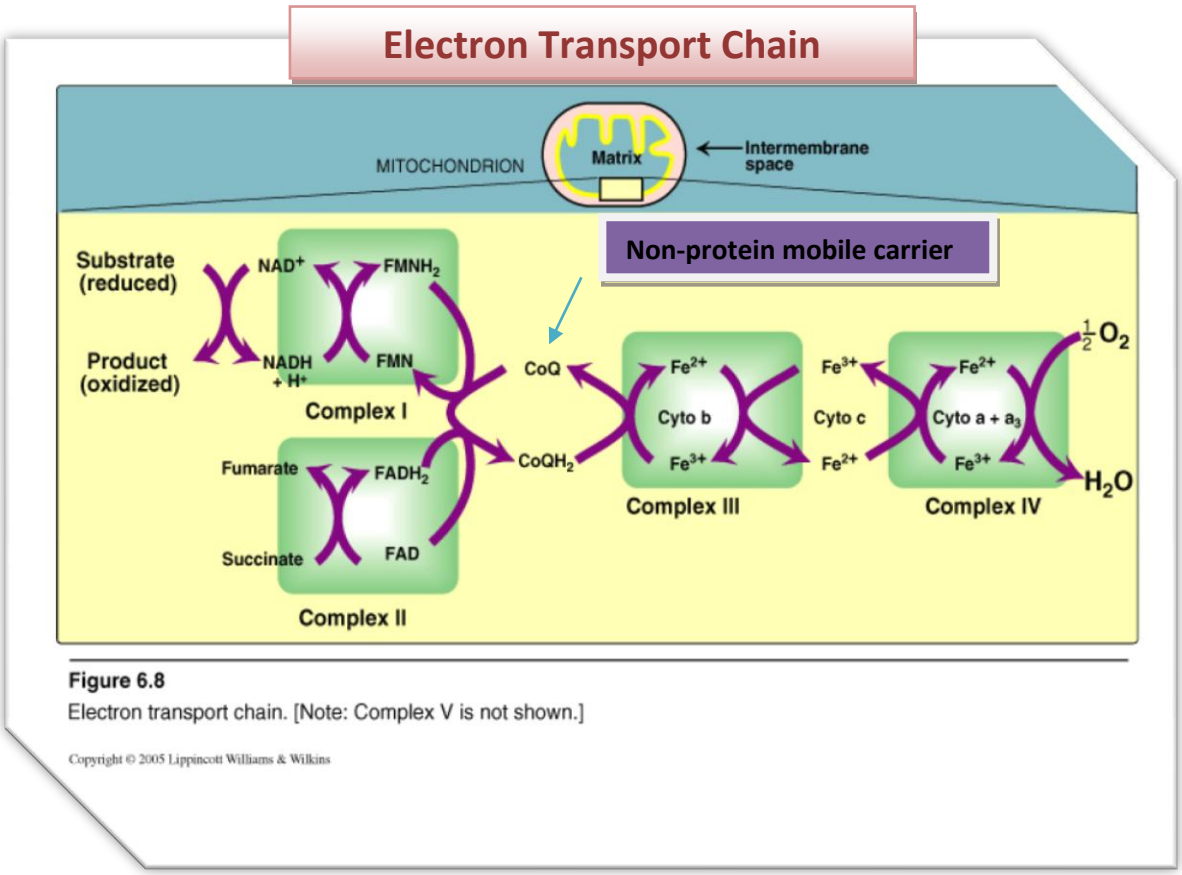

Figure 6.8
Electron transport chain. [Note: Complex V is not shown.]

Electron transport and ATP synthesis are tightly coupled processes

The Respiratory Chain

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❖ Mitochondria :

1) **Outer membrane:** contains special pores Freely permeable to most ions and small molecules

2) **Inner membrane:** highly convoluted to increase surface area ⟶ cristae

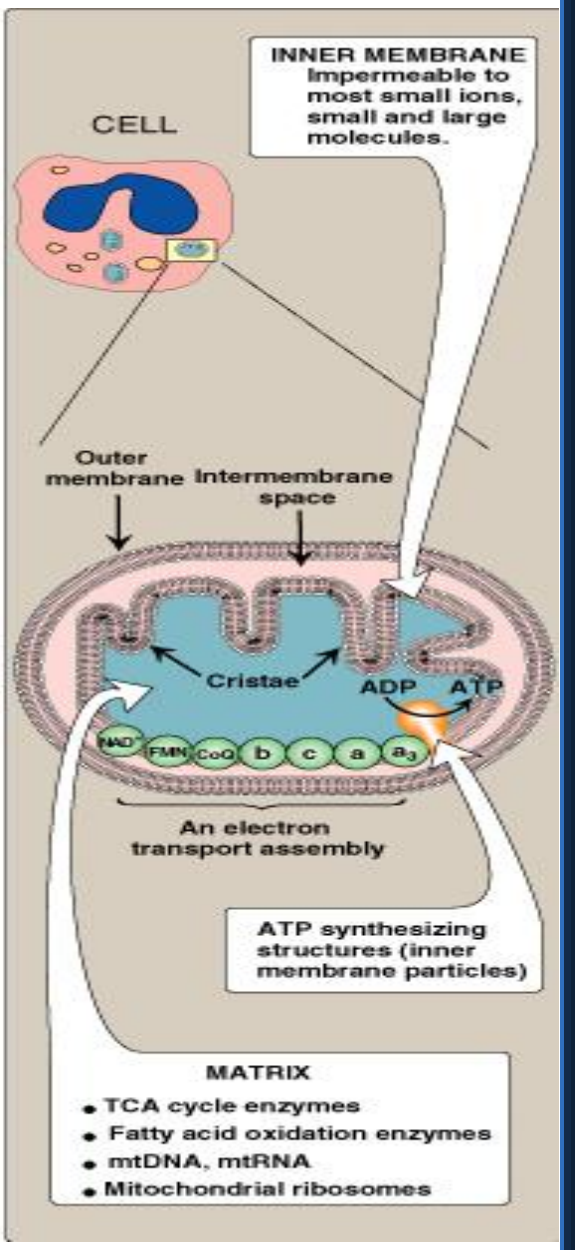
- Unusually rich in proteins ⟶ half are directly used in electron transport and oxidative phosphorylation

❖ Need specialized carriers or transport systems for impermeable:

- Ions: H^+, NA^+, K^+
- Small molecules: ATP, ADP, pyruvate, metabolites for mitochondrial function.

❖ **ATP synthase complexes:** protein complexes containing domains

- protrude into the matrix and span entire membrane

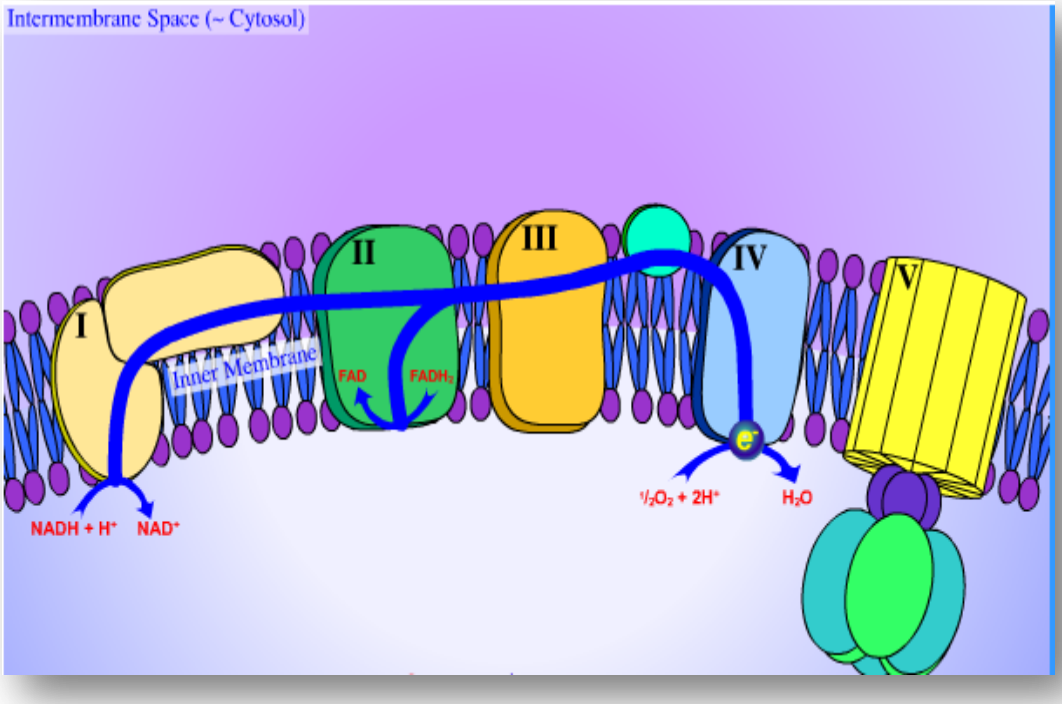


3) **matrix:** get-like solution ⟶ 50% is protein

1. Enzymes: oxidation of pyruvate, amino acids, fatty acids responsible for TCA cycle
2. Oxidized coenzymes ⟶ hydrogen receptors (NAD^+ and FAD)
3. ADP and P_i
4. Mitochondrial DNA and RNA and ribosome synthesis of glucose, urea and heme

The Respiratory Chain

Electron Transport Chain



- made of enzyme complexes : I, II, III, IV on the inner mitochondria membrane
- each complex donates electrons to mobile carriers
- carrier receives electrons from an electron donor and donates them to the next complex producing energy slowly
- also called the respiratory chain because it requires O_2
- electrons combine with o_2 and protein to form water
- all members of the chain are protein except coenzyme Q

❖ reactions:

1. formation of NADH : NAD^+ is reduce to NADH
   - Enzyme: dehydrogenases
   - reaction: 2 electrons + 1 proton (from substrate) + NAD^+ → NADH + H^+
2. Complex I: receives NADH, most reduce complex
   - Enzyme: NADH dehydrogenase → has a tightly bound coenzyme contains several iron – sulfur centers → necessary for transfer of H to coenzyme Q
   - Coenzyme: FMN → flavin mononucleotide
     $FMNH_2$ → when it accepts ($2 e^- + 2 H^+$)
3. Complex II: receives $FADH_2$, dose nit produce H^+
   - Enzyme: succinate dehydrogenase
4. Coenzyme Q: a quinine derivative with hydrophobic tail accepts H atom from $FMNH_2$ and $FADH_2$ links both flavoproteins to the cytochromes
5. Complex III: cytochromes b and a, receives electrons from coenzyme Q
   - Cytochromes: is a heme group + iron atom
   - Iron atom is reversibly converted from Fe^{3+} to Fe^{2+} reversible electron carrier
6. Cytochromes c
7. Complex IV: cytochromes a + a_3 or cytochromes oxidase
   - The only electron carrier which molecular oxygen can react directly with the heme iron
   - Contain bound copper for the following reaction to occur :
     2 electron + molecular O_2 + free portions → H_2O
     - Enzymes: the free energy is released as electrons
       - Electrons are transferred as hydride ions (H^-) to NAD^+ or as hydrogen atom to FMN, coenzyme Q and FAD or as electrons to cytochromes
     - Free energy: is used for phosphorylation of ADP to ATP
       - The excess is used for the reaction or produced as heat
       - NADH → 3 ATP (pump 3 H^+ from complex I, III, IV)
       - $FADH_2$ → 3 ATP (pump $2H^+$ from complex III, IV)

Phosphorylation:

1) **Proton pump :** **electron transport pumps protons (H^+) across the inner mitochondrial membrane to the intermembrane space**

- **Causes an electrical gradient (outside→more positive)**
- **Causes a PH gradient (outside→ lower PH)**
- **The proton gradient generates energy to drive ATP synthesis**
- **A common intermediate that couples oxidation to phosphorylation.**

2) **ATP synthase: complex V Has two domains**

❖ **F_0:**

- **membrane spanning Domain**
- **The protons reenter the matrix Through F_0 and rotate it.**

❖ **F1 :**

- **Extra membranous domain**

✓ **Note: electron movements :**

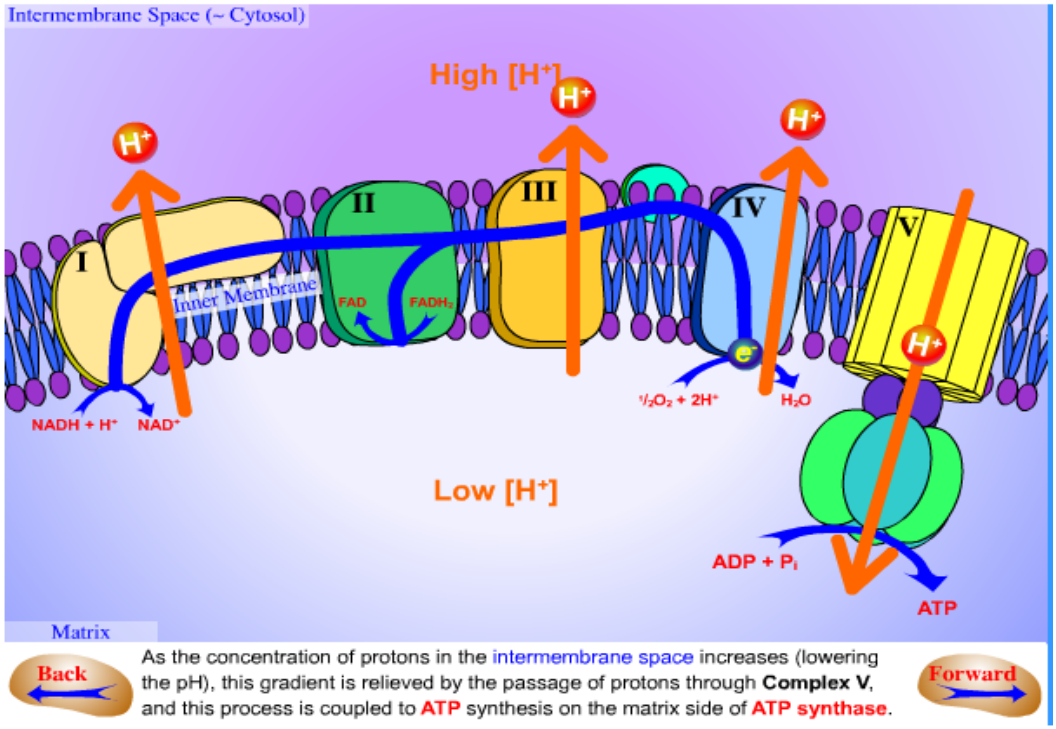
Electron transport chain → proton pump → crosses inner mitochondria membrane

↑ ↓

Matrix← F_1 ← F_0 of complex V ← Electrical gradient and PH ←inter membrane space

- **Undergoes conformational Changes after F_0 is rotated**
  - Catalytic activity is then activated
  - ATP synthesis from ADP + Pi
  - dissipating the PH and electrical gradients

The Respiratory Chain



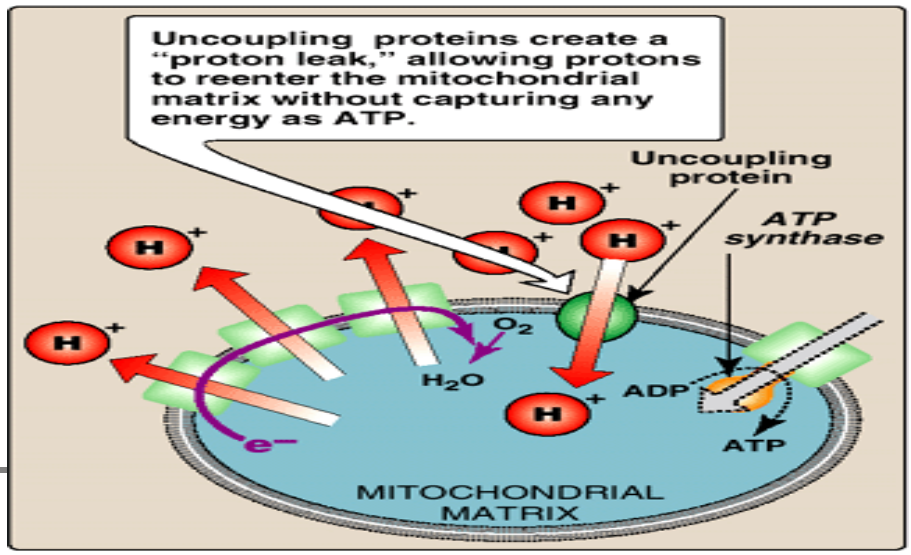
Factors affecting phosphorylation and oxidation:

a) Respiratory control:

1. **Oligomycin: drug that binds to F0 domain**

- **Closes H+ demands and prevents reentry into the matrix**
- **Prevents reentry of protons into the matrix and phosphorylation**
- **PH and electrical gradient cannot be dissipated**
- **Difficulty pumping protons against the steep gradient prevent oxidation**

2. **Decreased availability of ADP or P_i**



b) Uncoupling proteins (UCP) :

- **Location: inner mitochondrial membrane**
- **Function: the proteins create a "proton leak"**
  Allow protons to reenter the matrix without energy being captured as ATP.
- **UPC1: found in brown adipocytes of mammals (humans and animals)**
- **Function: activation FA oxidation and heat production**
- **90% of respiratory energy for thermogenesis (unlike white fat)**
- **Responds to: cold, at birth, arousal in hibernating animals**
- **In humans: little brown fat except infants**
- **Doesn't play a major role in energy balance**
- ✓ **UPC2 and UPC3 are found but unknown significance**

c) Synthetic uncouplers :

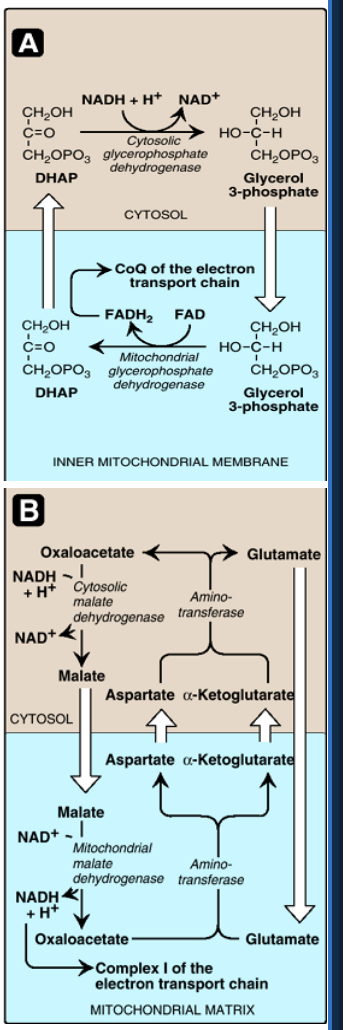
- **Increase the permeability of inner mitochondrial membrane to protons**
- **Uncouple oxidative phosphorylation by readily diffusing**
- **Causes electron transport to proceed rapidly without a proton gradient**
- **Energy is released as heat rather than being used to synthesize ATP (ATP is not synthesized)**

Ex:

1) **2,4 – dintrophenol : a lipophilic protein carrier .**
2) **Toxic dose of aspirin and salicylates : accompanied by fever .**

MEMBRANE TRANSPORT SYSTEM :

A) ADP: cytosol → adenine nucleotide carrier → inner mitochondrial membrane
ATp : mitochondria → adenine nucleotide carrier → cytosol
P_i : cytosol → phosphate carrier → mitochondria



b) Reducing equivalents:
NADH: inner mitochondrial membrane lacks an NADH transport protein passes indirectly by two different shuttles.

1) Glycerophosphate shuttle :

cytosol → NADH + H^+ → NAD^+ + 2 e^-

inner mitochondrial membrane → 2 e^- + Glycerophosphate degeneration

produces : $FADH_2$ → COQ → 2ATP / cytosolic NADH oxidized .

2) Malate – Aspartate shuttle :

cytosol → NADH + H^+ → NAD^+ + 2 e^-
matrix → 2 e^- + Malate degeneration
produces : NADH → 3 ATP / cytosolic NADH oxidized

The Respiratory Chain

Apoptosis :programmed cell death.

Pores are formed on the outer membrane of mitochondria

Cytochrome c leave through the pores to the intermembrane space then cytosol.

In the cytosol: Cytochrome c + proapoptotic factors → activates a family of proteolytic enzyme (the caspases) → cleavage of key protein → morphological and biochemical change → Apoptotic cell death.

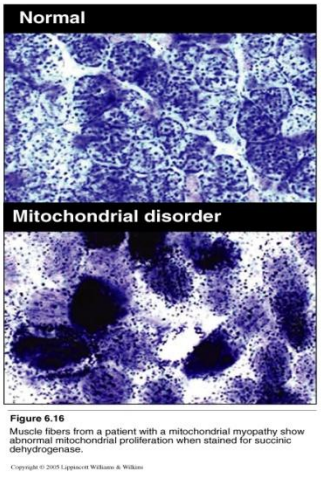


Figure 6.16
Muscle fibers from a patient with a mitochondrial myopathy show abnormal mitochondrial proliferation when stained for succinic dehydrogenase.

- **-Inherited defect in oxidative phosphrylation :**

Mt DNA : codes polypeptides required for oxidative phosphorylation

Polypeptides are synthesized in the mitochondria .

Mutation rate is 10 times higher than nuclear DNA

Mutation:- defects in oxidative phosphorylation affects tissues with high ATP requirment

Ex: CNS , skeletal and heart muscle , kidney ,liver

Disease :- mitochondrial myopathy – leber hereditary optic neuropathy : neuroretinal degeneration

Damage to the optic nerve – bilateral loss of central vision .