



مقدم من فريق أفق الطبي



Medical Biochemistry
Carbohydrate Metabolism

Asst. Prof. Mohammed Hasan Eleyan

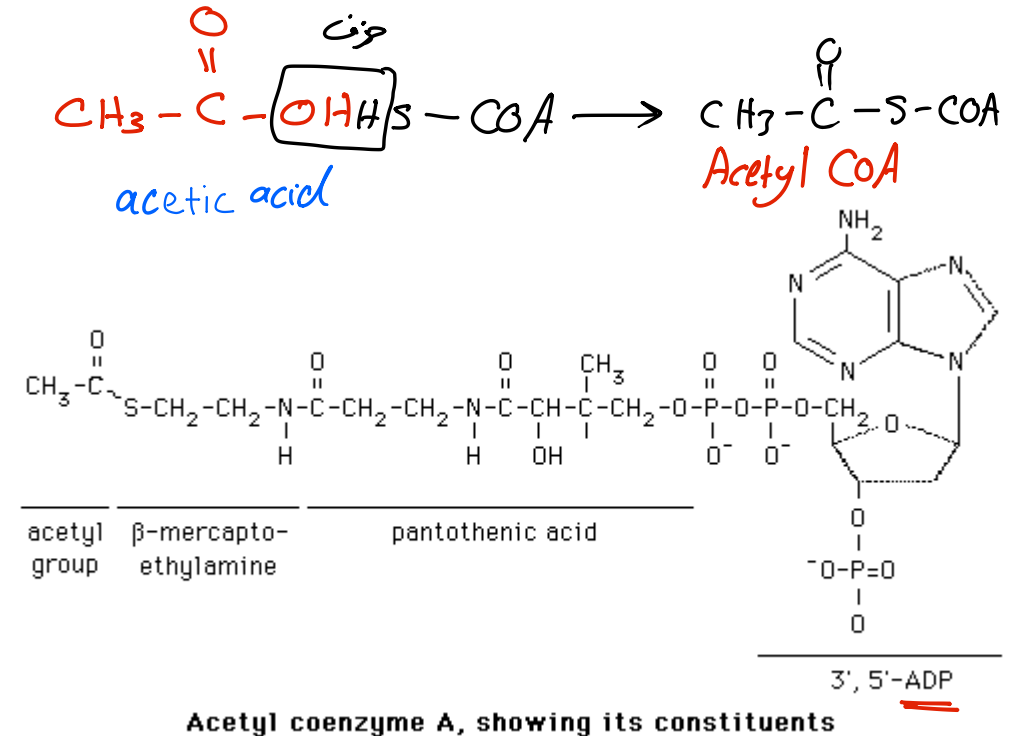
Faculty of Medicine

Al-Azhar University-Gaza

The structure of Acetyl CoA consists of two parts.

1. Acetyl group
2. Coenzyme A

- Beta-mercaptoethylamine
- Pantothenic acid (vitamin B5 derivative)
- Phosphate
- 3', 5'-adenosine diphosphate



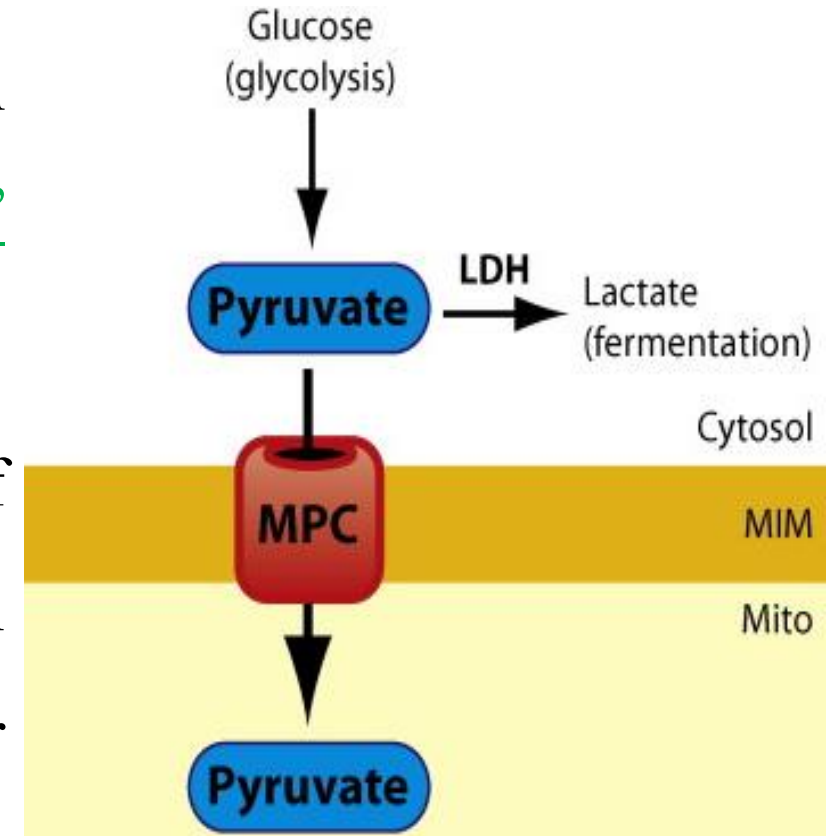
Phosphated

ADP

Mitochondrial pathway for glucose oxidation

Mitochondrial pathway for glucose oxidation

- Complete oxidation of glucose occurs in both Cytosol (glycolysis) and mitochondria (Krebs' cycle).
- In the presence of O₂, pyruvate (the end product of glycolysis in cytosol) passes by **m**itochondrial **p**yruvate **c**arrier (**MPC**) into mitochondria (to enter citric acid cycle)



Mitochondrial pathway for glucose oxidation

remove the H remove carboxyl group

- Oxidative decarboxylation of pyruvate to Acetyl-CoA.

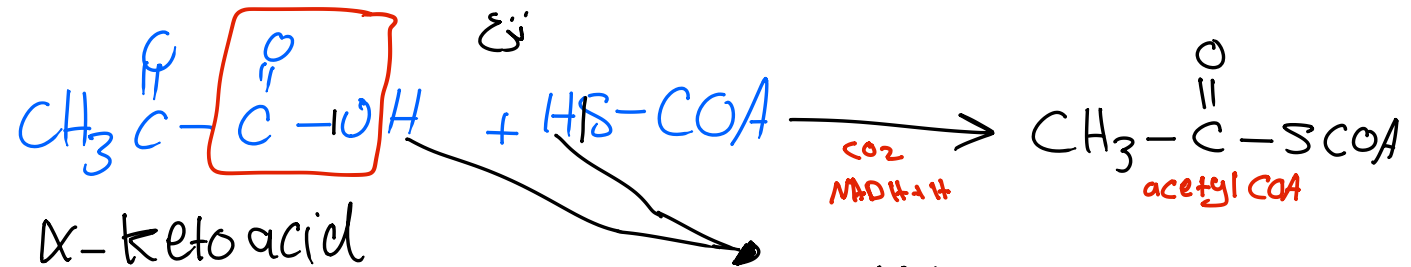
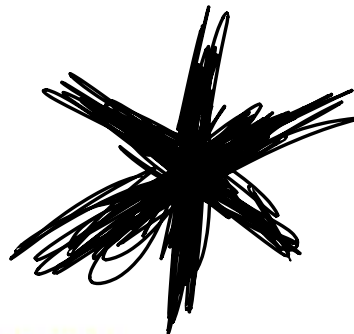
- Acetyl CoA is then oxidized completely to CO₂, H₂O through Krebs' cycle.

- Pyruvate decarboxylation is the link between glycolysis and the citric acid cycle.

ورج تطيع كمان او electrons التي راح يتم تحييدهم على الـ FAD و NAD وتدخل في سلسلة نقل الإلكترون electron transport chain

عنما نصل هذه الخطوة تعتبر حلقة وصل بين حلقة كربس و الـ glycolysis التي بتخبر في السيتوسول

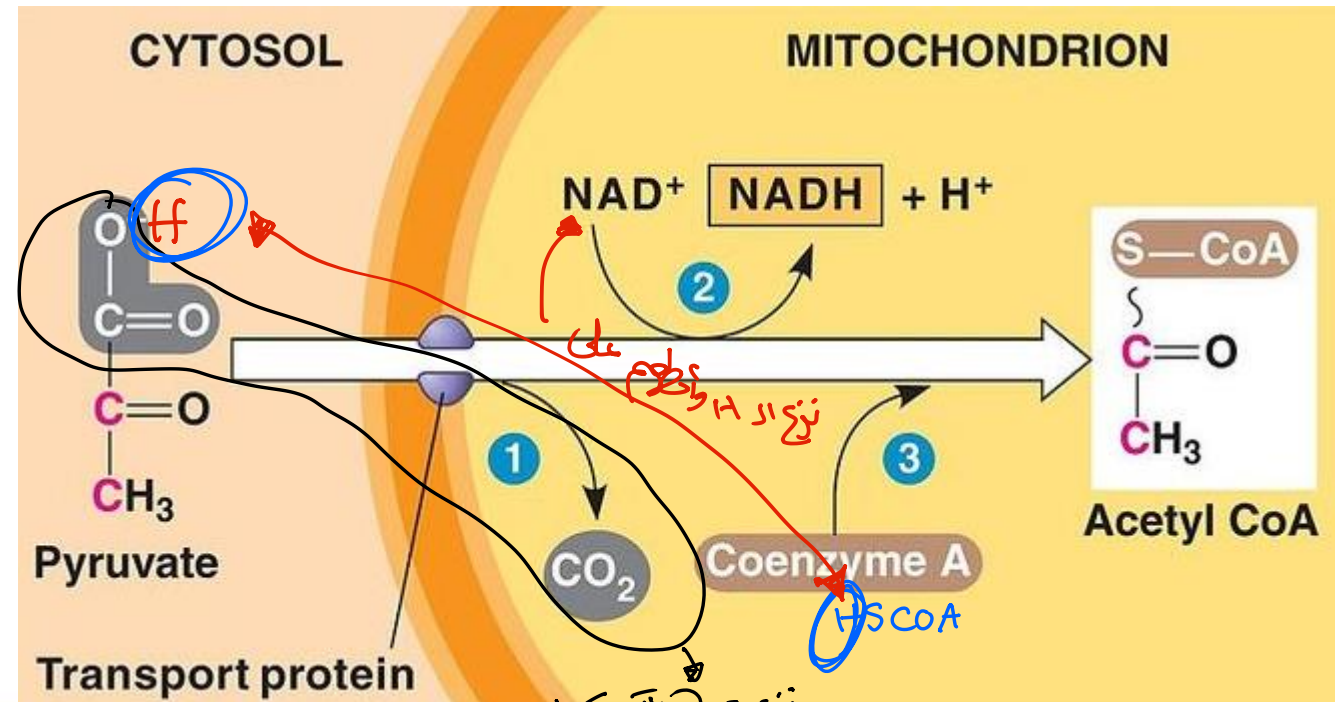
decarboxylation (إزالة نزع مجموعة الكربوكسيل)



دافع انفسهم على
FAD و NAD

Oxidative decarboxylation of pyruvic acid

- Oxidative decarboxylation of pyruvic acid is catalyzed by:
- Pyruvate dehydrogenase (PDH) complex



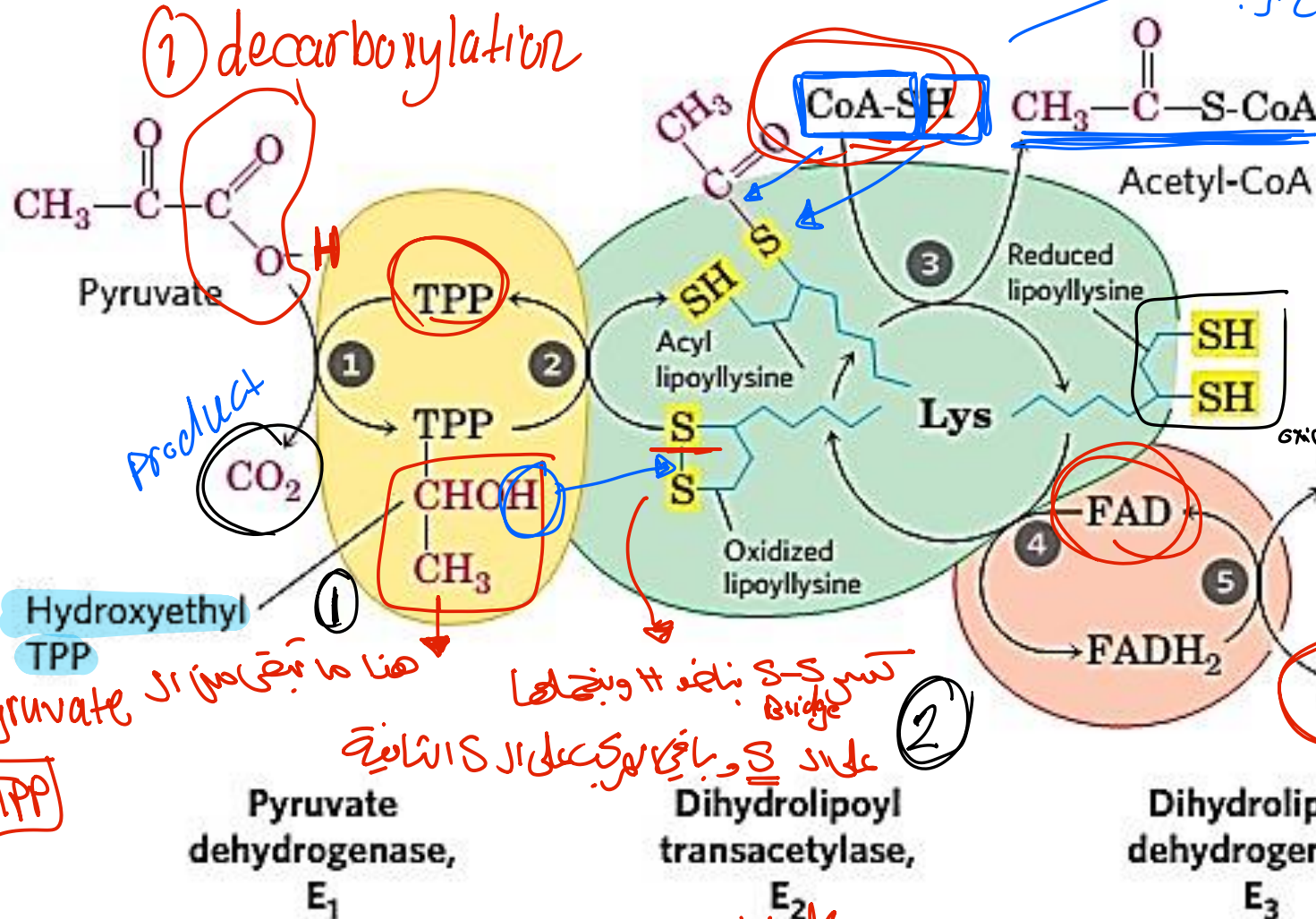
Pyruvate dehydrogenase (PDH) complex

پیتھو کیٹون ڈی هائیدرو جیناز

site	Multienzyme complex	Five coenzymes	Irreversibly
mitochondrial matrix.	1. Pyruvate decarboxylase 2. Dihydrolipoyl transacetylase 3. Dihydrolipoyl dehydrogenase.	1. Vitamin B1 = Thiamin pyrophosphate = TPP. 2. Lipoic acid 3. Coenzyme A = CoASH. 4. FAD. 5. NAD+.	The irreversibility of this reaction prevents the formation of pyruvate from acetyl-CoA, explain why glucose cannot be formed from acetyl-CoA. بعد، افسوس سے اس glucose اس acetyl-CoA وليس الجلوكوز

Products
 1- CO_2 2- Acetyl-CoA 3- $\text{NADH} + \text{H}^+$

Oxidative decarboxylation of pyruvic acid



ال H₂ له ترتب به ال S
 دتله SH و COA له ترتب
 باقي المركب و منتج
 (product)

(3)

كول د reduced
 يعني SH و S
 و بي اصول oxidized
 باخذ ال H من
 ال S و ال H من
 ال FAD و بي FADH₂
 جيسه كملهم على NAD⁺
 بعدا له كلف التفاعل

(5)

(4)

(2)

كس S-S بنافه H و بنافه
 على ال S و باقي المركب على ال S ال اضافيه

هنا ما باقي من ال
 pyruvate تم كلفه ال
 TPP

ع ال نقل ال
 acetyl group

KREBS' CYCLE

- Definition: series of reactions in which acetyl CoA is oxidized into CO_2 , H_2O and energy.
- Citric acid cycle (CAC), tricarboxylic acid cycle (TCA) or Catabolism of acetyl CoA

↓
KREBS' cycle
Product
أول منتج

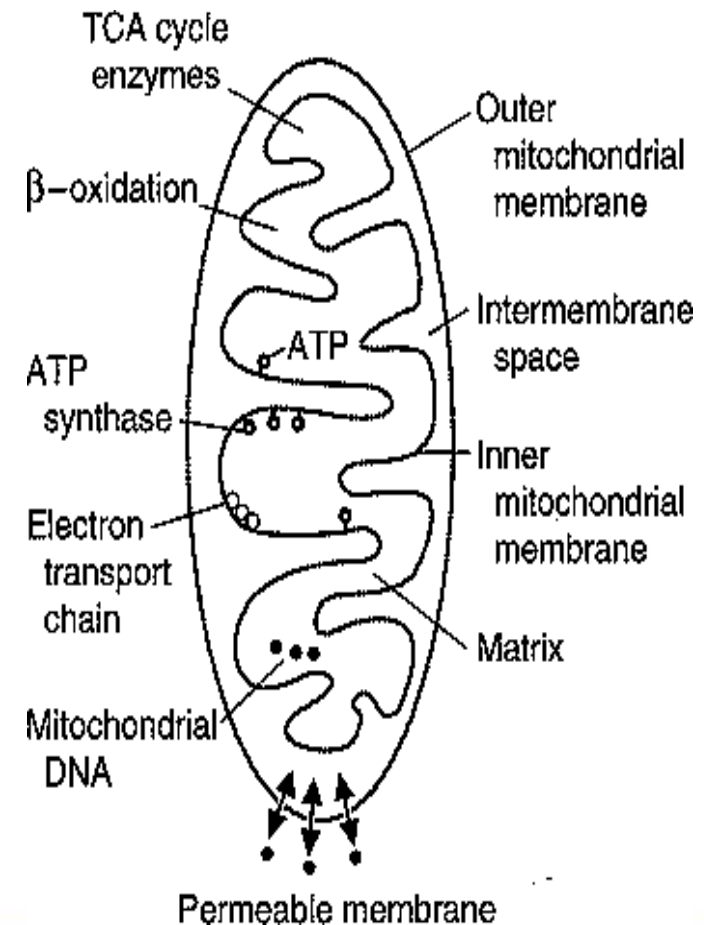
↓
products
لأنه في هذه الدورة في بعض الأحيان
carboxylic acid
التي تحتوي على 3 مجموعات حمضية
(3 COOH)

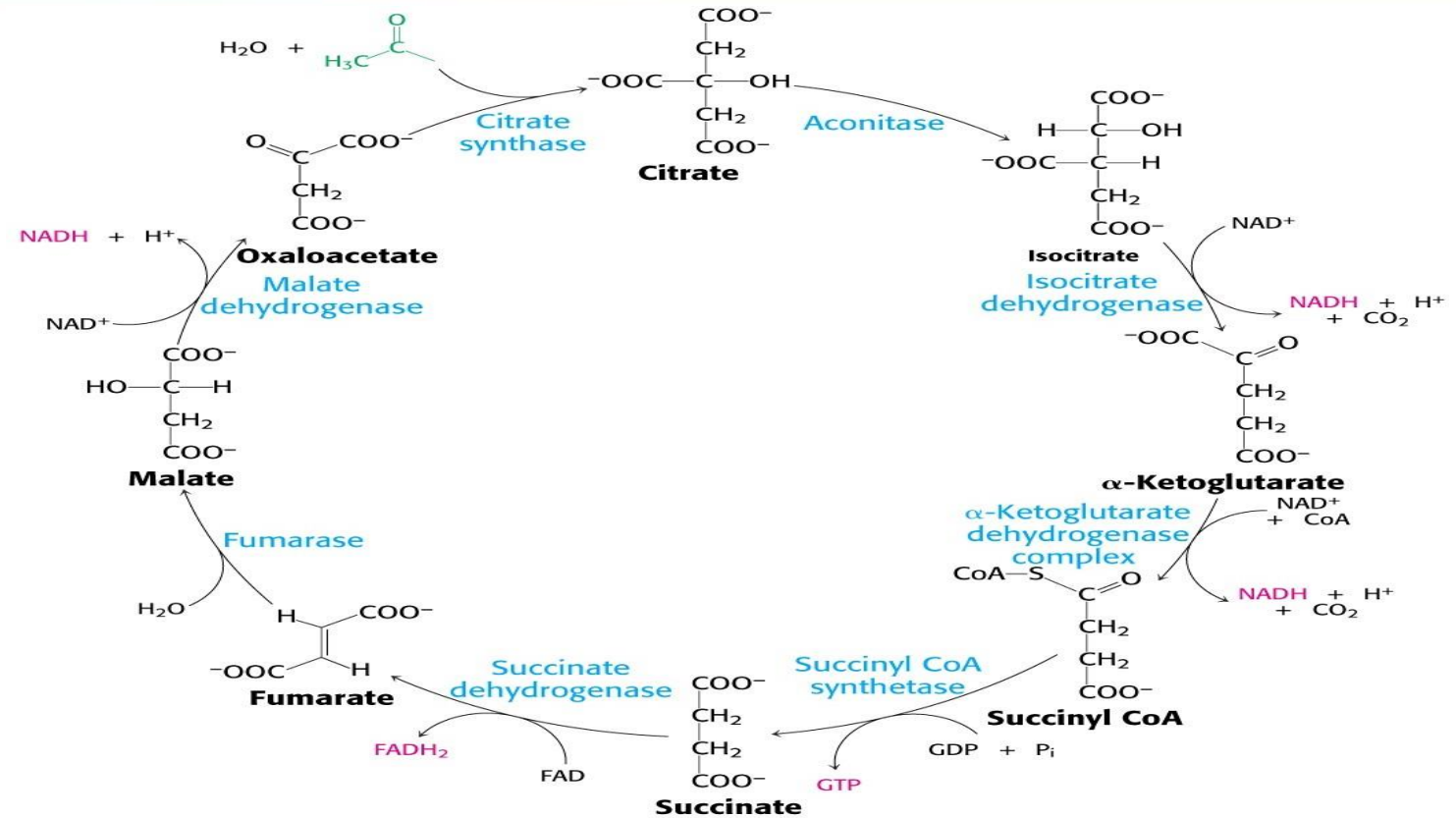
↓
oxidation
energy + CO_2
لأنه في هذه الدورة في بعض الأحيان
acetyl CoA

Krebs' Cycle

عند من التفاعلات المتتالية التي من خلالها يتم
energy + CO₂ ← oxidation ← acetyl CoA

- Site: The enzymes of the TCA cycle are found in the **mitochondrial matrix** except **succinate dehydrogenase** which is tightly bound to the inner mitochondrial membrane (forms complex II of the respiratory chain).
- During the reactions of the cycle, coenzymes (NAD⁺ and FAD) are reduced and subsequently reoxidized by the respiratory chain with the formation of ATP.





TCA cycle steps

Once **acetyl CoA** is formed in the mitochondria, the Krebs cycle starts in 8 steps.

Steps: Our City Is Kept Safe And Sound From Malice.

الخطوات 8 خطوات
 substrate واد product واد enzyme واد هذا التفاعل يجمع
 NAD و FAD يجمع GTP يعني بشكل عام أما structure غير معلوم

Acetyl-CoA is a crucial entry point for the Krebs cycle (TCA cycle), and glucose is just one of the many ways cells can generate it.

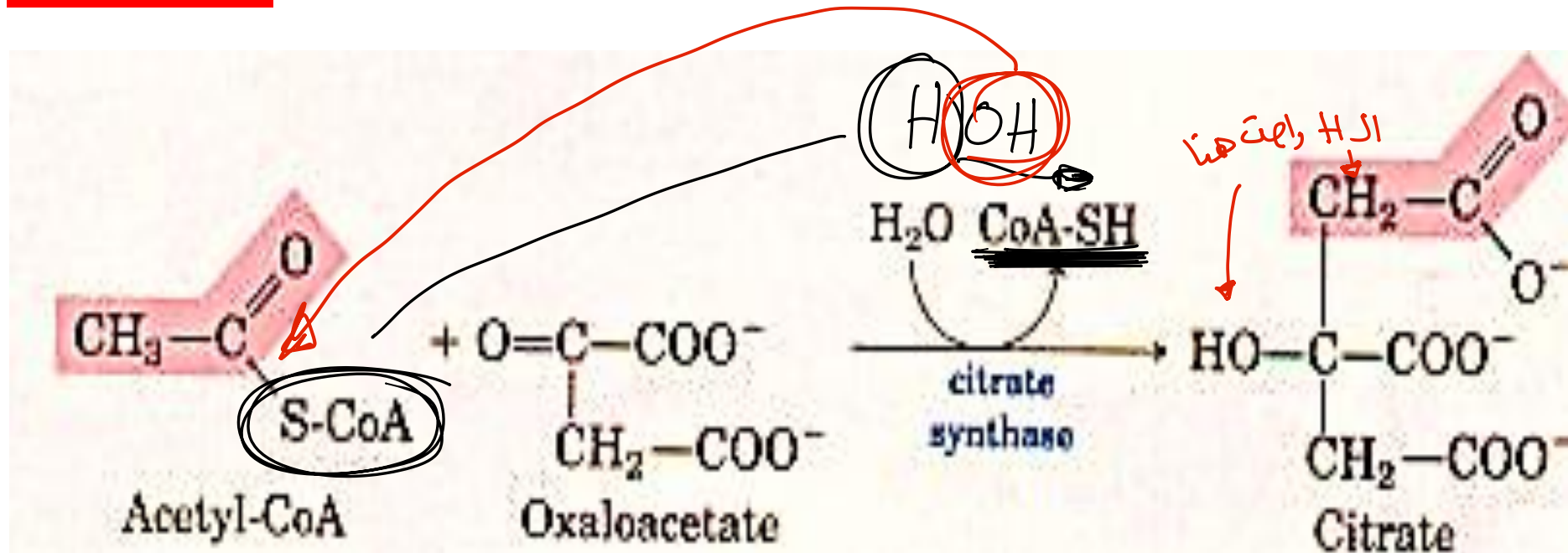
Fatty Acids, Ketone bodies (acetone, acetoacetate, and β -hydroxybutyrate), Alcohol, and Amino Acids

يعني في كثير خطوات تامة تنتج الـ Acetyl CoA من مس عن الـ glucose زي ههون

1-Condensation of acetyl CoA and oxalacetate

یعنی بستیقہ املا

- Condensation of acetyl CoA and oxalacetate by citrate synthase to give citric acid

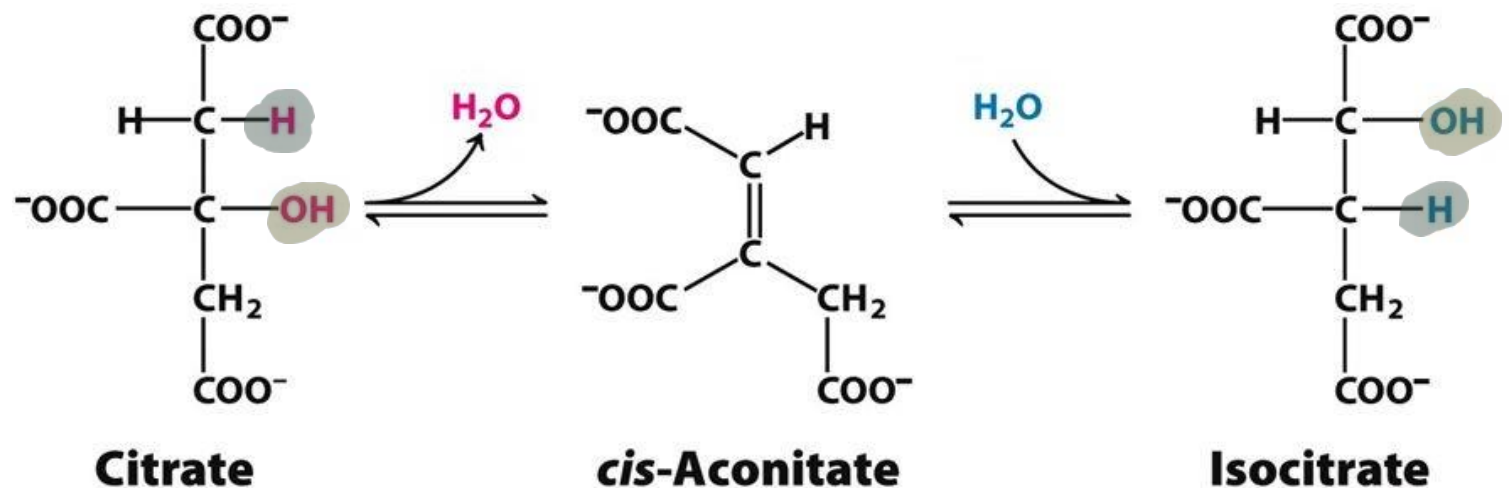


Irreversible TCA

intermediate

2-Interconversion of citrate, cis aconitate to isocitrate:

- The reaction is catalyzed by aconitase enzyme.
- This reversible reaction represents the removal and addition of H_2O to this tricarboxylic acid



الخطوة ! نه بدلي ابدل بين ال OH وال H
عن طريق ال isocitrate

(interconversion)

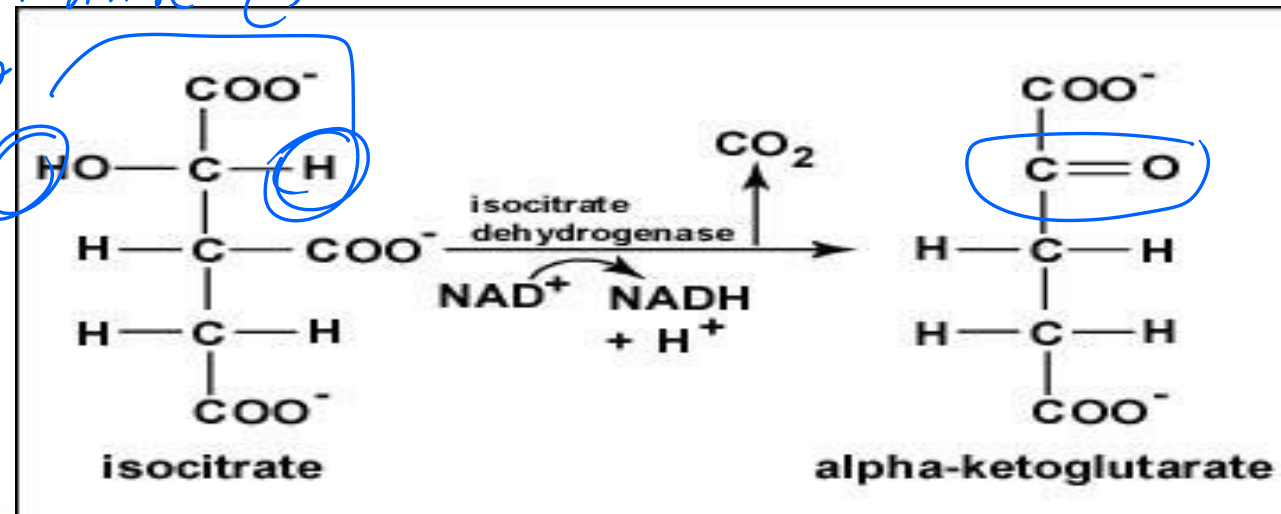
3-Conversion of isocitrate to α -ketoglutarate:

- Isocitrate dehydrogenase catalyzes the **irreversible** oxidative decarboxylation of isocitrate, yielding α -ketoglutarate, **NADH** and release

removal of H

CO_2 .
↑
بنتج كربوكسيل
على صورة

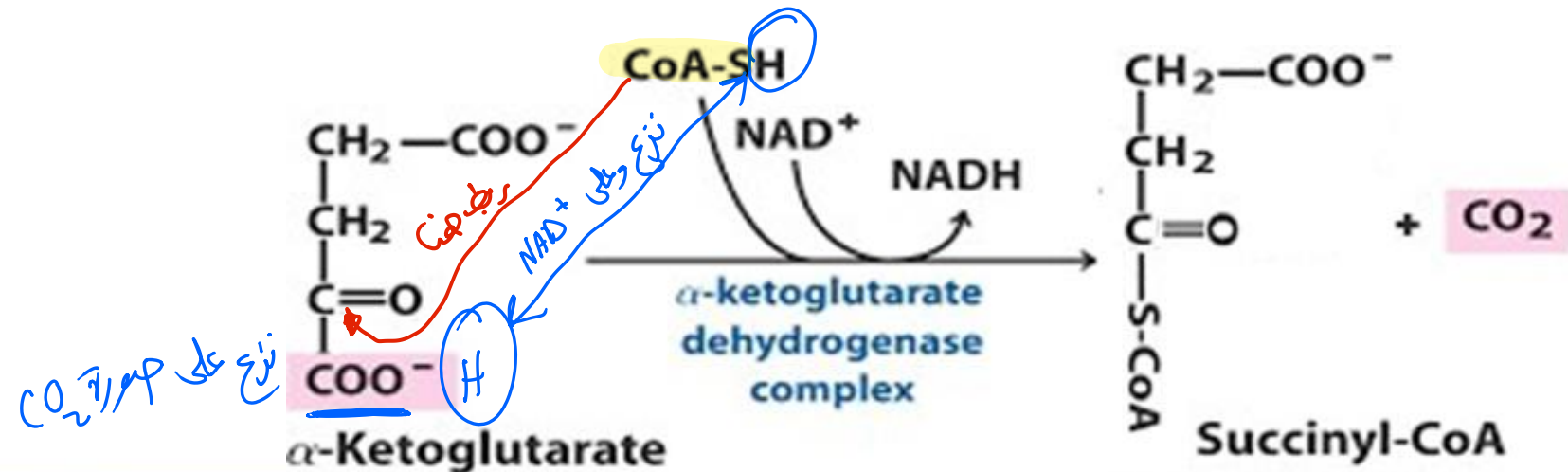
نزع oxidative
وإزالة H على NAD^+
حتى ينتج
 $\text{NADH} + \text{H}^+$



موجودة على
تربوطة X

4-Conversion of α -ketoglutarate to succinyl CoA

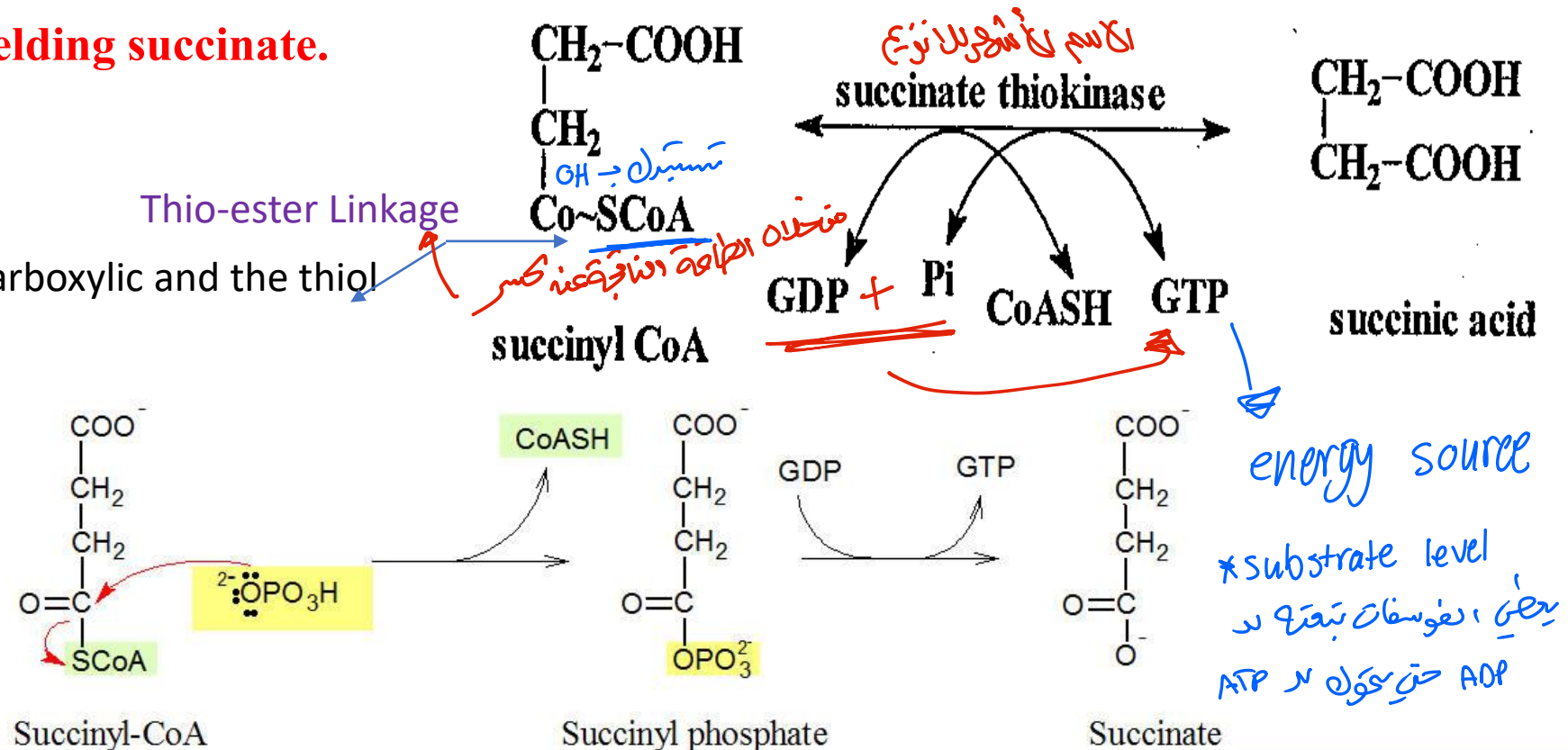
1. Oxidative decarboxylation of α -ketoglutarate is catalyzed by **α -ketoglutarate dehydrogenase**, similar to PDH, requiring the same 5 coenzymes (TPP, lipoic acid, FAD, NAD⁺ and CoASH.).
2. The reaction **releases the second CO₂** and produces the **second NADH** of the cycle.



5-Cleavage of succinyl-CoA

- Succinyl-CoA synthetase (succinate thiokinase) cleaves the high-energy bond of succinyl-CoA, yielding succinate.

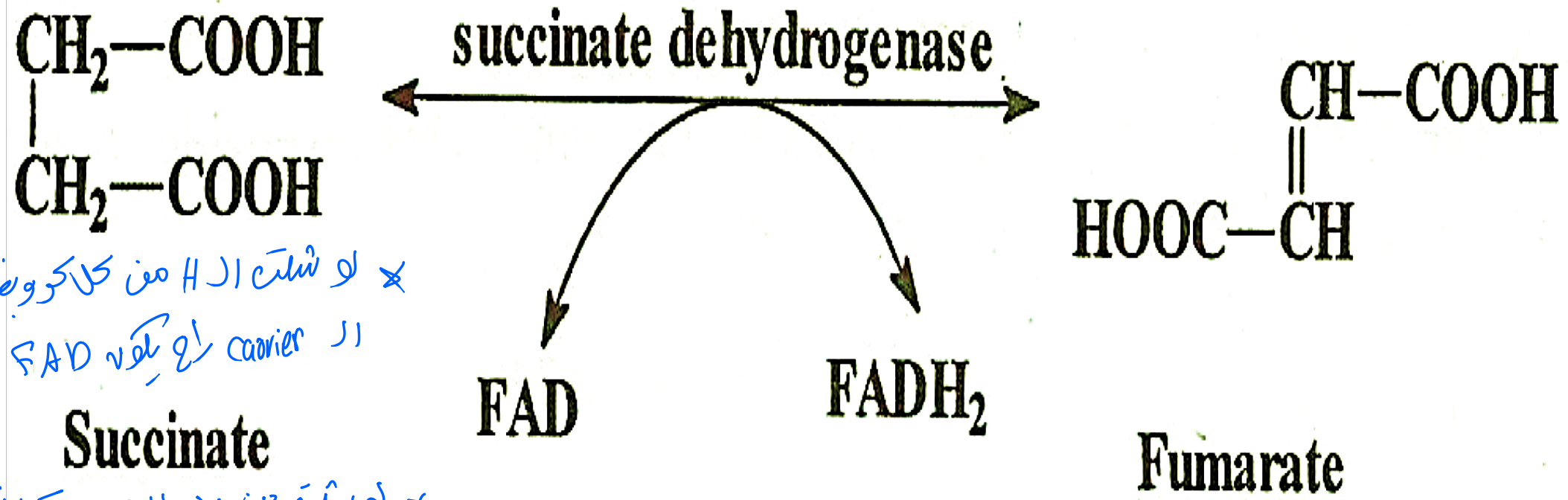
- It includes all of bonds between a carboxylic and the thiol group of CoA



6-Succinic acid to fumarate

نزع H

- **Dehydrogenation of succinic acid to fumarate by succinate dehydrogenase:**



* لو شلت H من كل كربون واحدة
carrier (أو FAD)

Succinate

FAD

FADH₂

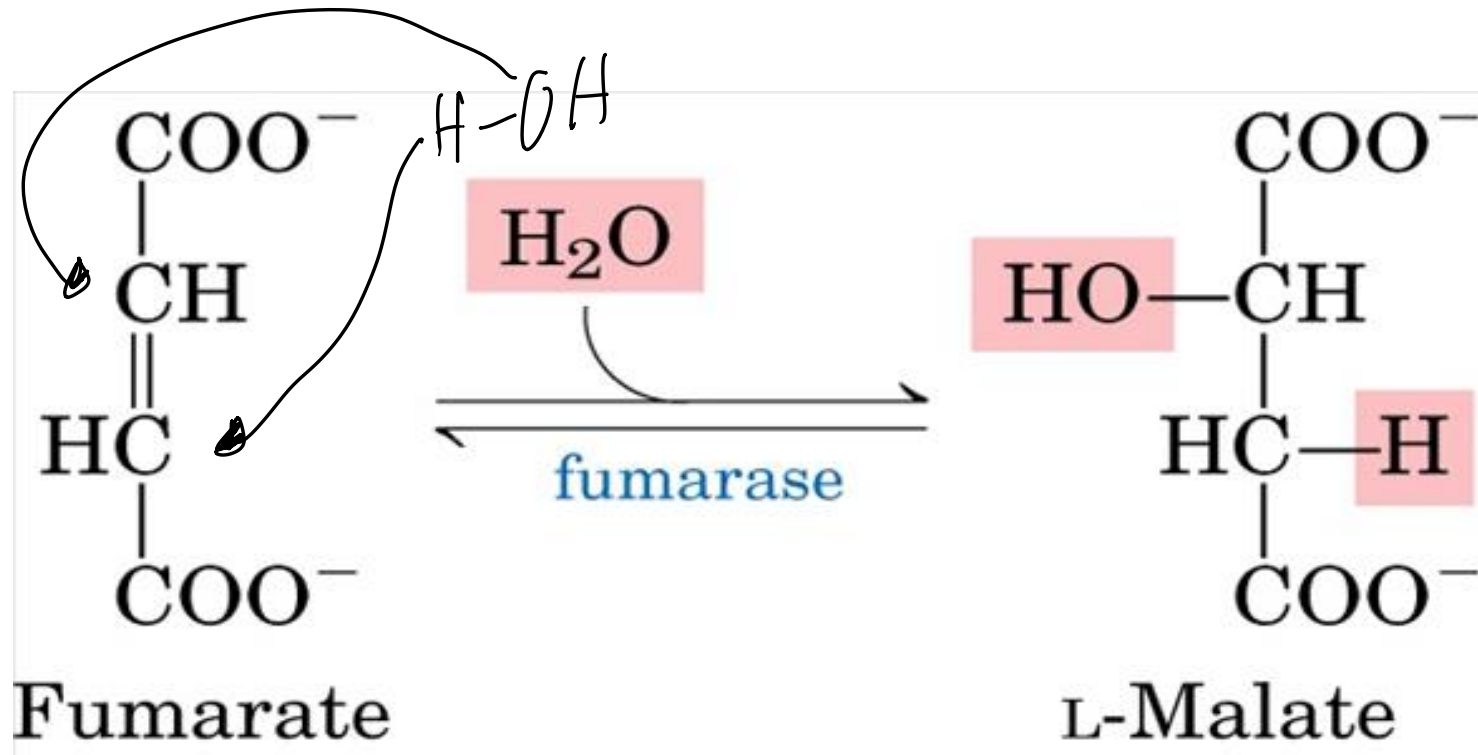
Fumarate

* لو شلت من 2H من كل كربون واحدة
carrier (أو NAD)
M.ELEYAN

7-Hydration of fumaric acid

Handwritten note: $\text{H}^+ \text{ & } \text{H}_2\text{O}$

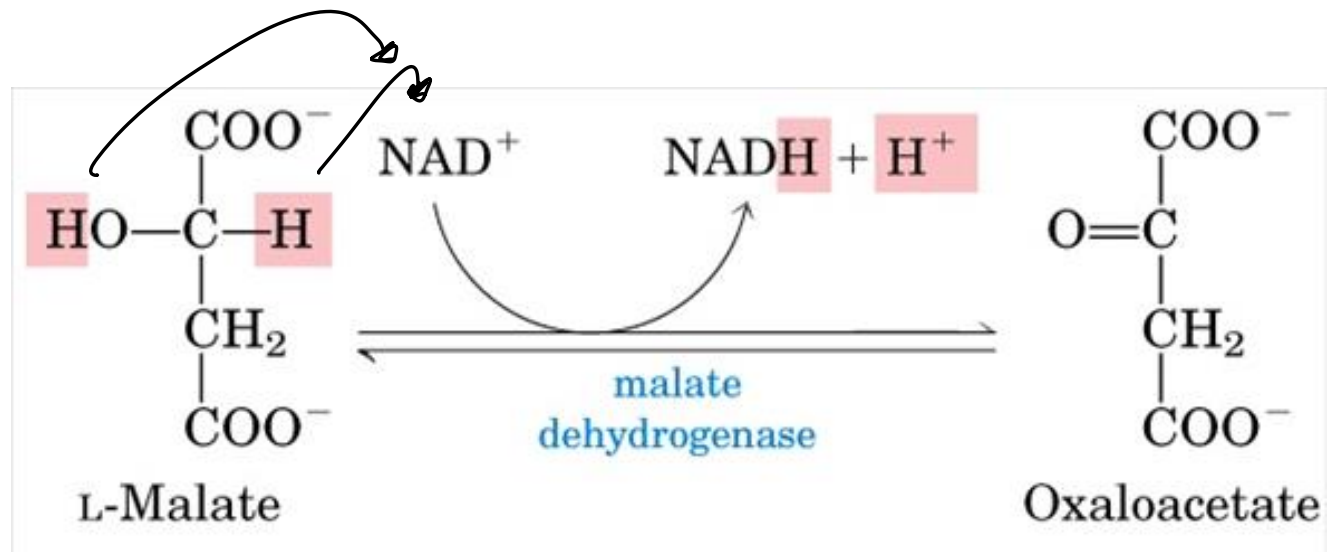
Fumarate is hydrated to malate catalyzed by **fumarase**.



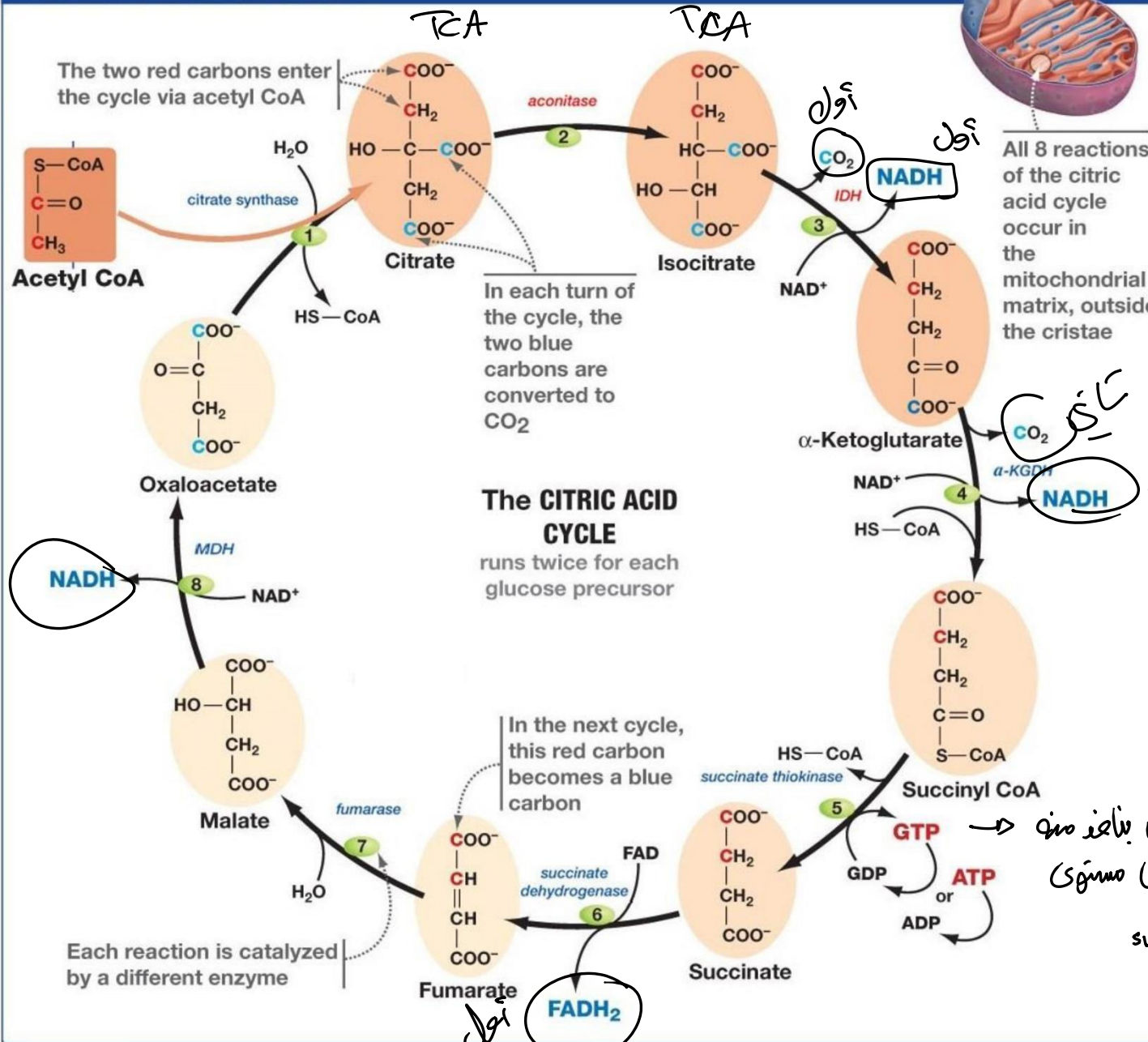
8-Oxidation of malate and regeneration of oxaloacetate

- This reaction catalyzed by **malate dehydrogenase** produces the **third and final NADH** of the cycle.
- The **oxaloacetate** can further condense with another acetyl- CoA molecule and the cycle continues.

نُدخل من نفس الكربون



PROCESS: CITRIC ACID CYCLE



All 8 reactions of the citric acid cycle occur in the mitochondrial matrix, outside the cristae

تای
تای

اول تفاعل بناهذ منه
energy
substrate

Important Notes on TCA Cycle

Isocitrate Dehydrogenase (IDH) (Enzyme) : Isocitrate to α -ketoglutarate

- A **Key** Enzyme in the TCA Cycle
- IDH activity can be **stimulated** by a high **ADP/ATP ratio**. *activity تَبَعًا تَزِيدُ إِذَا كَانَ مَسْتَوًى ADP مَرْتَفِعَ يَعْنِي فِي low energy*
- IDH is **inhibited** by both **ATP** (high energy levels) and **NADH** (sufficient electron carrier).
- This enzyme **is not** under **hormonal regulation**, as the TCA cycle operates continuously in both fasting and feeding states to meet the cell's basic energy needs. *وَلَمْ يَكُنْ أَدْرَ Acetyl CoA مَصْرُوفًا مَعَهُ لِبَسَادٍ glucose فَيَنْتَفِعُ*

α - ketoglutarate dehydrogenase (Enzyme): α -ketogluterate to succinyl CoA

- Example of oxidative decarboxylation reaction.
- Requires the 5 coenzymes (TPP, lipoic acid, FAD, NAD⁺ and CoASH.).
- Inhibited by: succinyl-CoA, NADH, ATP

Succinyl-CoA synthetase (Enzyme): succinyl-CoA to succinate

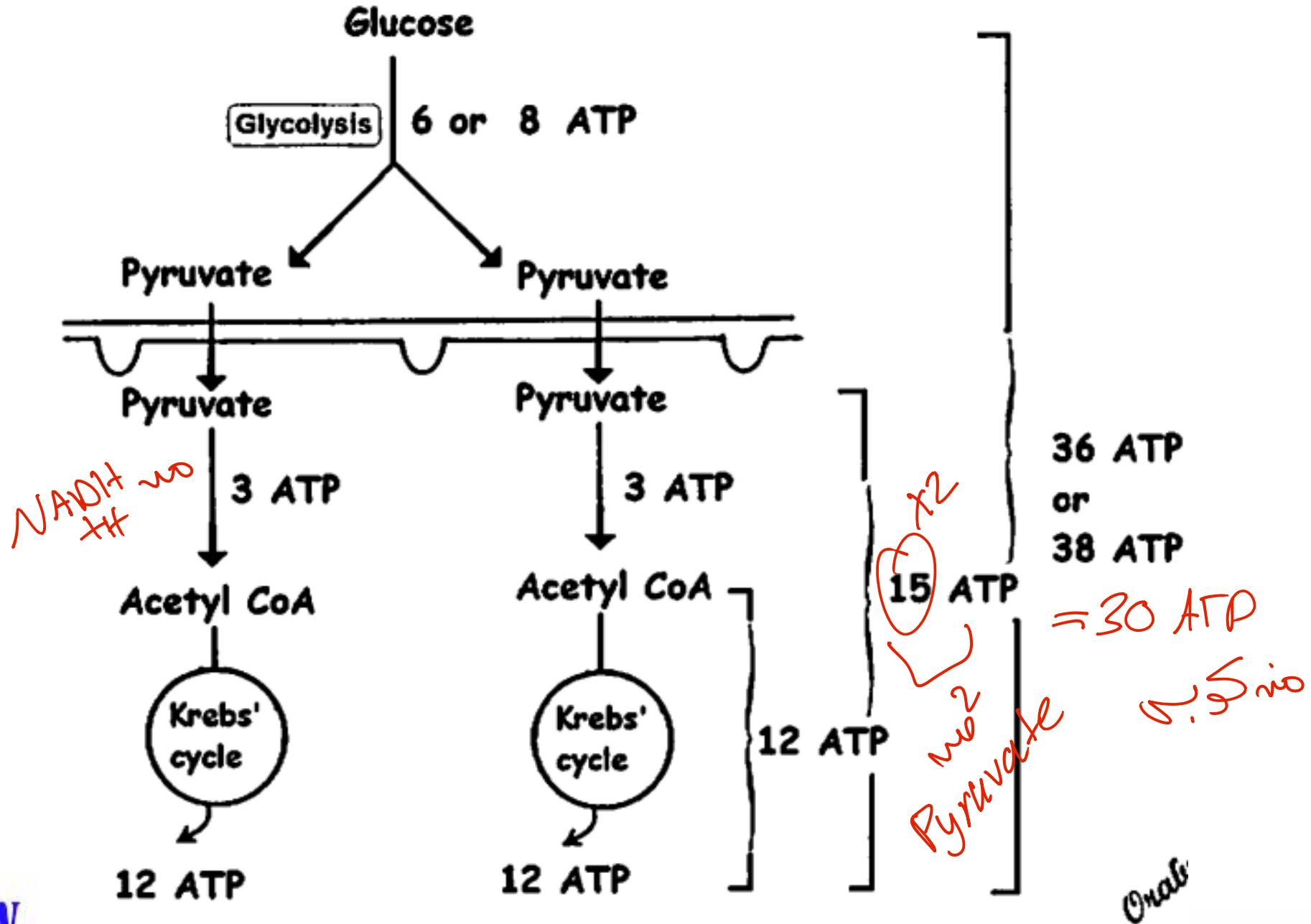
- Example of substrate level phosphorylation reaction as, it forms GTP by high energy bond from **succinyl-CoA**.
- This reaction is accompanied by phosphorylation of guanosine diphosphate (GDP) to guanosine triphosphate (GTP).
- The GTP thus formed then readily transfers its terminal phosphate group to ADP forming an ATP molecule.

Energy production of TCA:

Enzyme	Method of ATP production	No. of ATP
Isocitrate dehydrogenase	Oxidation of $\text{NADH} + \text{H}^+$ by respiratory chain phosphorylation	3 ATP
α -Ketoglutarate dehydrogenase	Oxidation of $\text{NADH} + \text{H}^+$ by respiratory chain phosphorylation	3 ATP
Succinyl CoA thiokinase	Substrate level phosphorylation	1 ATP
Succinate dehydrogenase	Oxidation of FADH by respiratory chain phosphorylation	2 ATP
Malate dehydrogenase	Oxidation of $\text{NADH} + \text{H}^+$ by respiratory chain phosphorylation	3 ATP
Total =		12 ATP

Oxidation of one molecule of acetyl CoA in TCA produces 12 ATP

Complete
oxidation



Orabi

Energy production of complete oxidation of one molecule of glucose:

- Glucose oxidation → 36 or 38 ATP.
- Pyruvate oxidation → 15 ATP. (12 Krebs cycle + 3 Acetyl CoA)
- Acetyl CoA → 12 ATP

Amphibolic Nature of the TCA cycle

- Citric acid cycle is an **amphibolic** (both catabolic + anabolic) in nature.
- The catabolic functions: 12 ATP for Acetyl CoA
 - It is the **final pathway** for **complete oxidation** of all food-stuffs **CHO, lipids and protein** which are converted to **acetyl CoA**.
 - It is the **major source of energy for cells** except cells without mitochondria as RBCs.

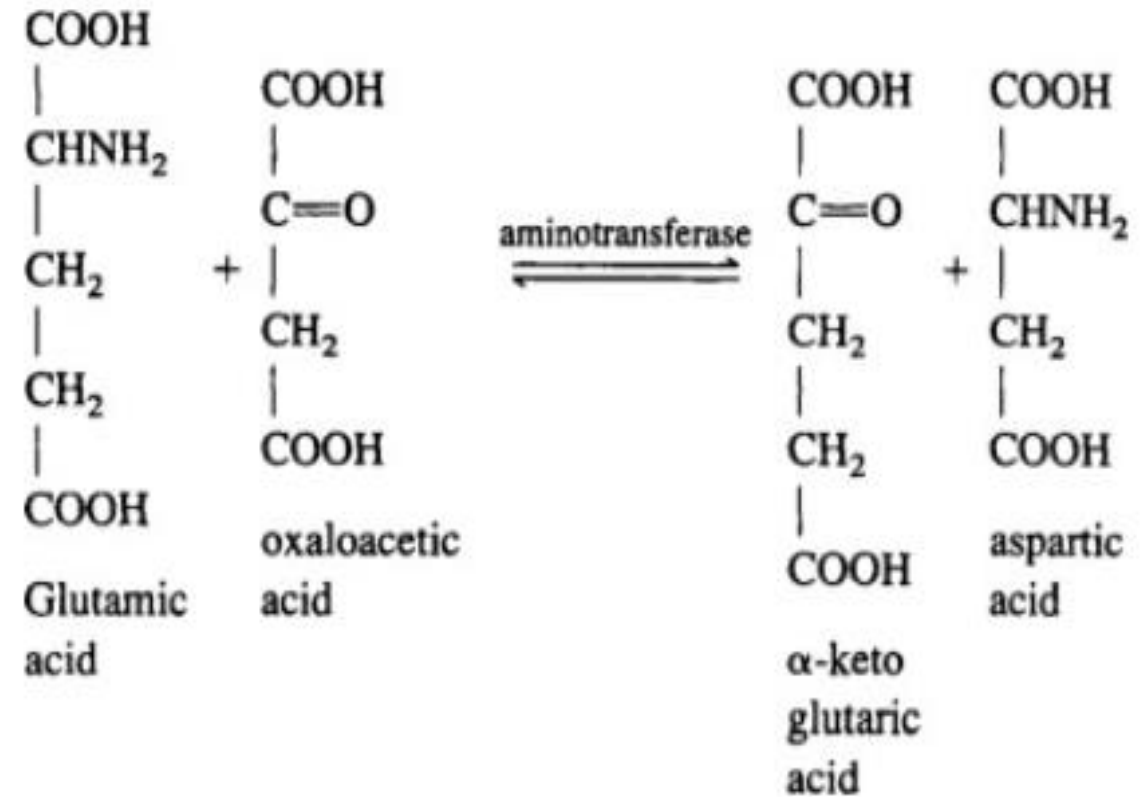
The anabolic functions (provides precursors for many anabolic pathways)

↓
 بتوفر intermediates
 بتدخل في بناء المركبات

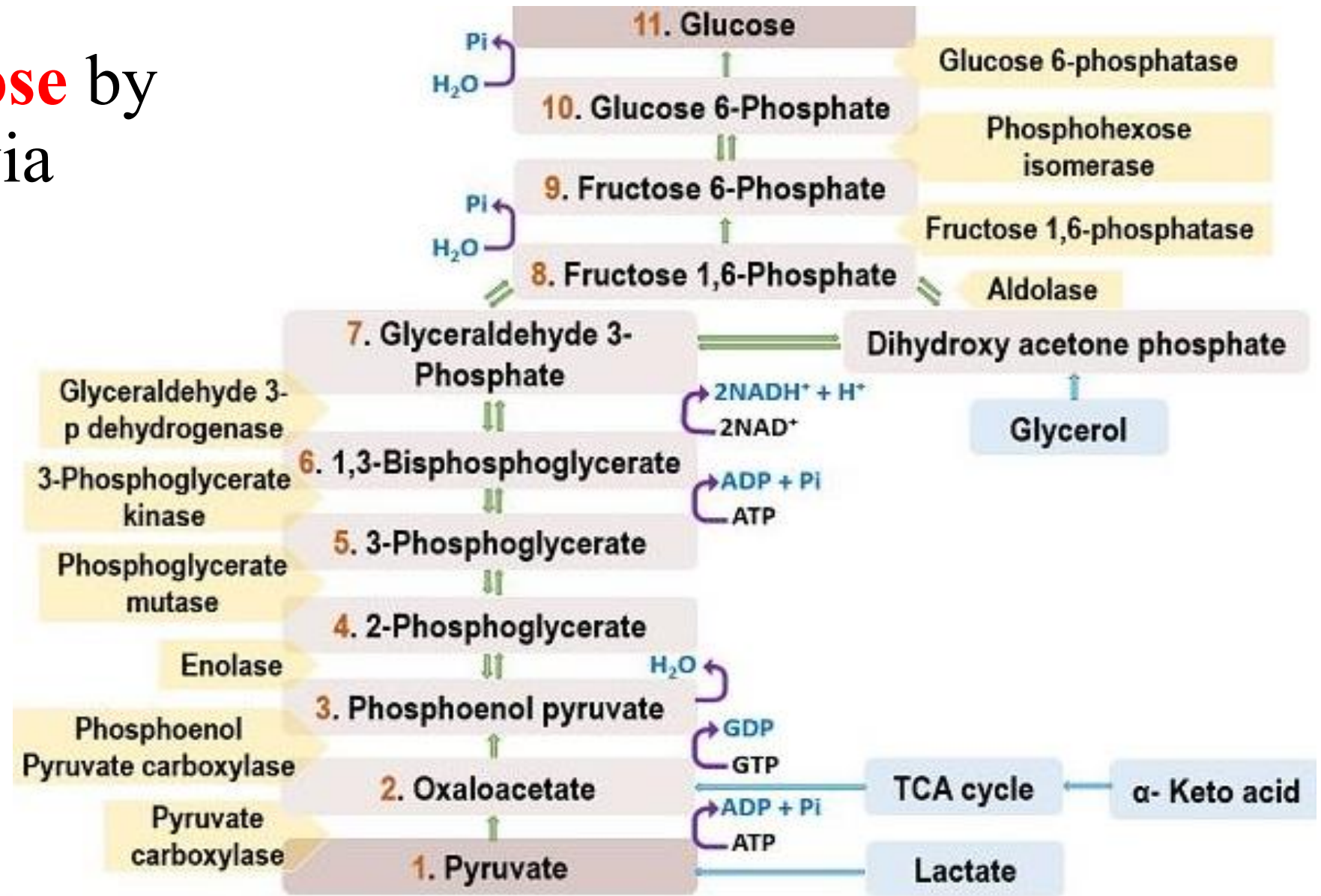
α -Ketoglutarate Transamination → Glutamate.

Oxaloacetate Transamination → Aspartate.

amino group
 نقل



Synthesis of **glucose** by gluconeogenesis via oxaloacetate.

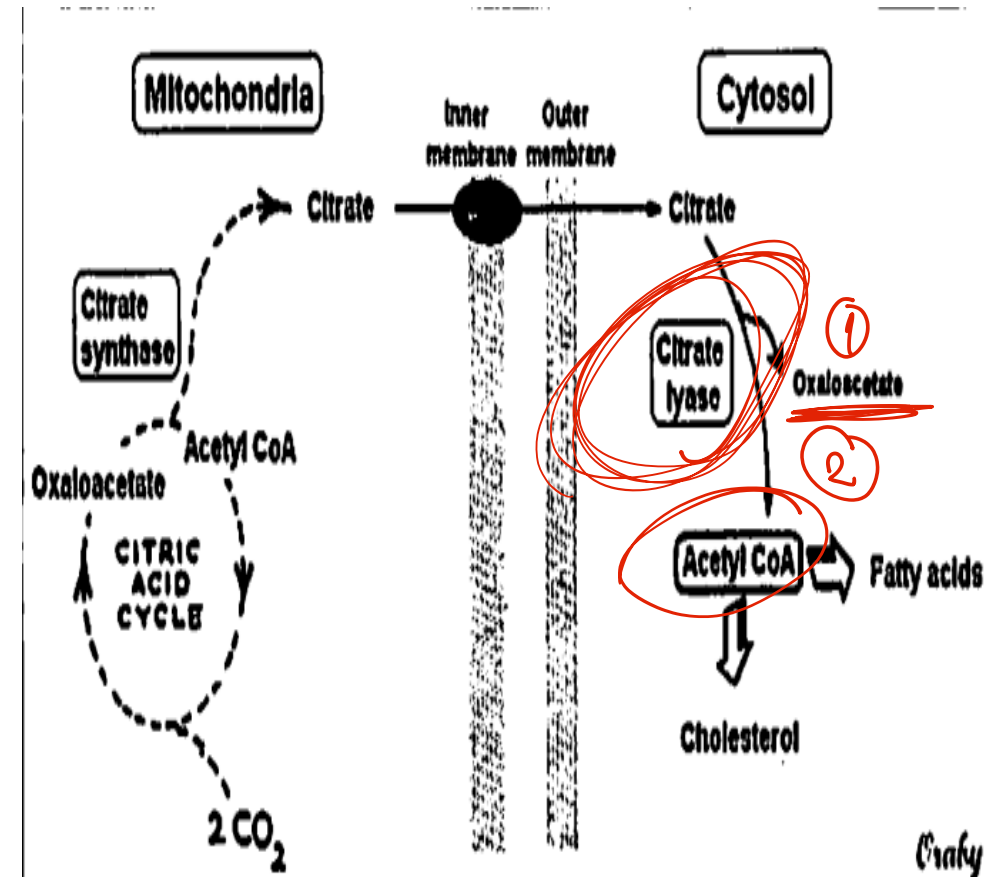


فatty acids و cholesterol من mitochondria الى cytoplasm diffusion

Fatty acids and cholesterol: from acetyl CoA (synthesized in cytosol)

- Acetyl CoA is produced in mitochondria.
- The inner mitochondrial membrane is impermeable to acetyl CoA.
- To overcome this impermeability, acetyl CoA combines with oxaloacetate to form citrate (diffuses to cytosol).
- Acetyl CoA becomes the building block for fatty acid synthesis in the cytosol
- $\text{citrate} + \text{ATP} + \text{CoA} \rightarrow \text{oxaloacetate} + \text{Acetyl-CoA} + \text{ADP} + \text{P}_i$

citrate
lyase

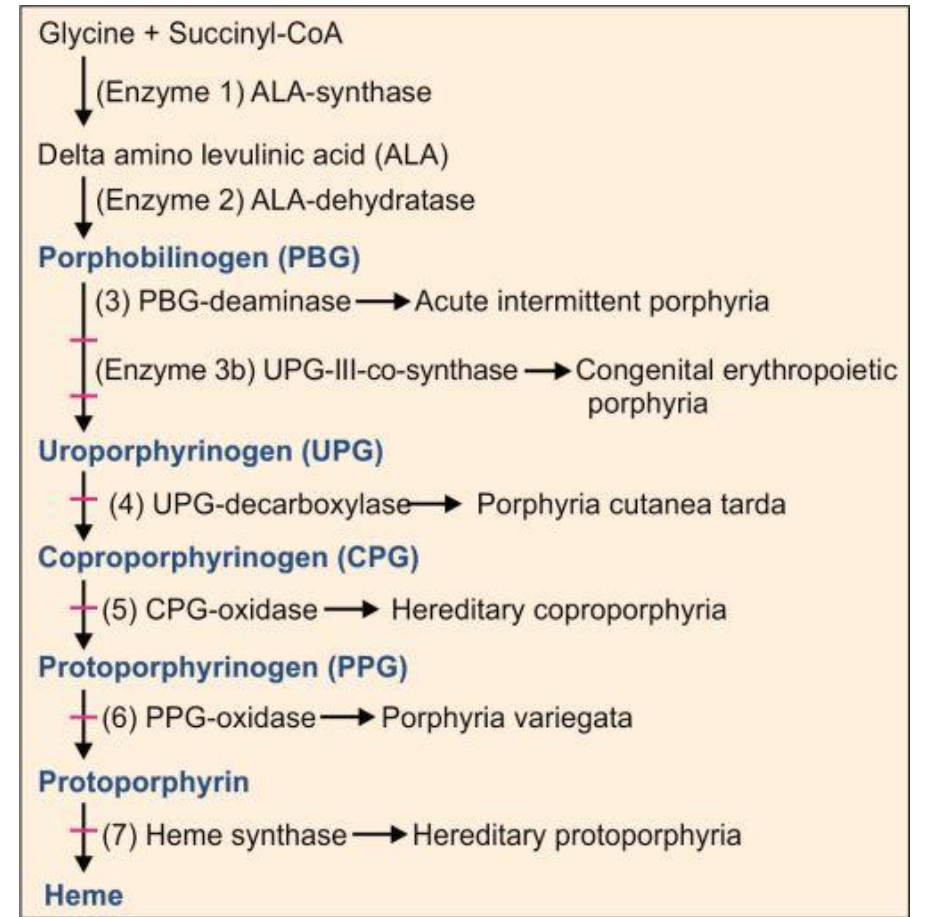


Craty

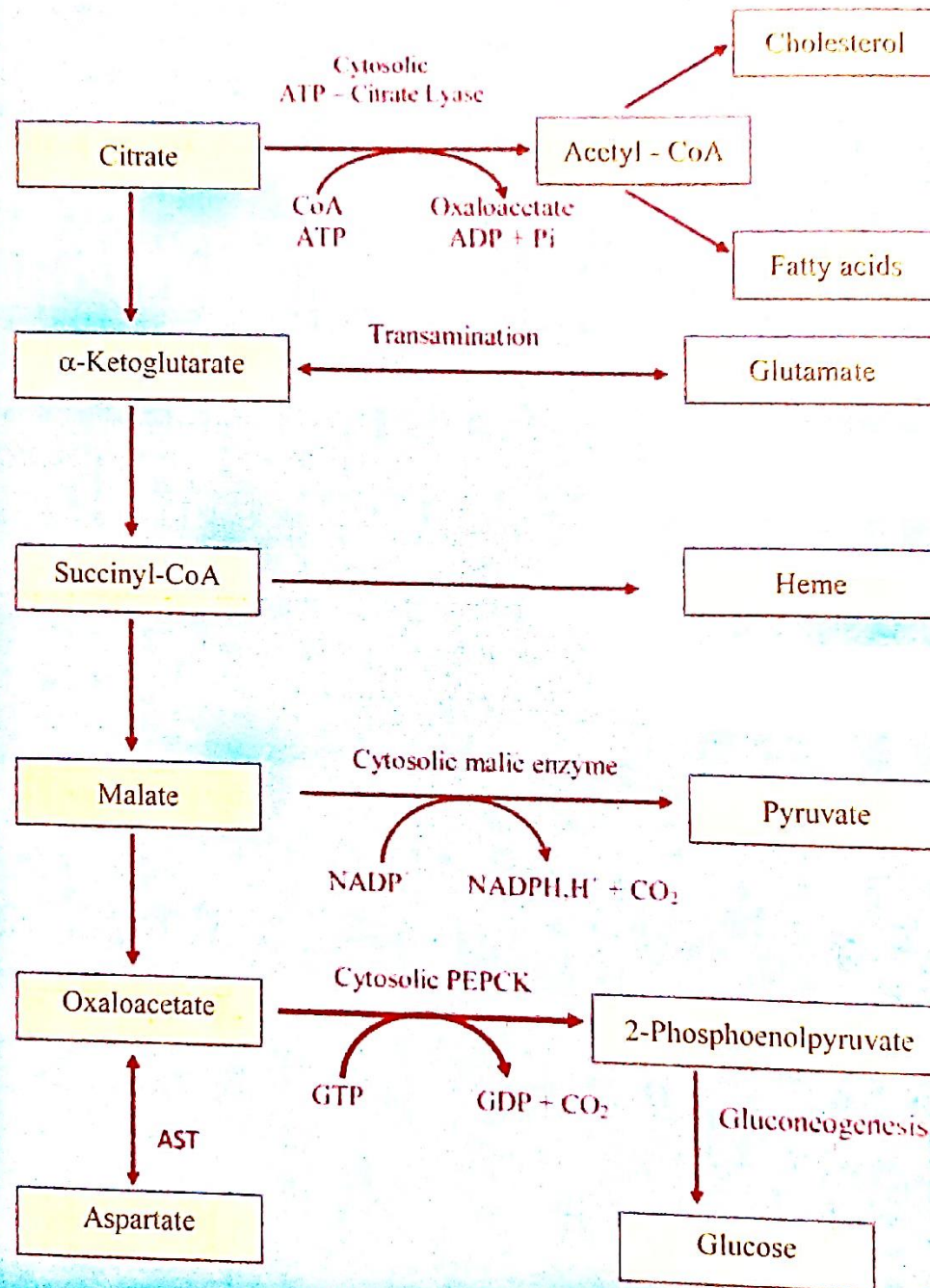
+ glycine

Succinyl CoA which is used
for perphyrine and HB
synthesis.

(Heme) / new Co



Importance of the Intermediates of TCA Cycle
(Anabolic Function)



Regulation of Citric Acid Cycle

1. The key enzymes: (Citrate synthase, Isocitrate Dehydrogenase, α -Ketoglutarate Dehydrogenase)

- Stimulated by: ADP and NAD^+

low energy $\rightarrow$ ATP

- Inhibited by: ATP and $\text{NADH} + \text{H}^+$

high energy ATP is inhib

2. The availability of O_2 : This is because in absence of oxygen, respiratory chain is inhibited leading to increase $\text{NADH} + \text{H}^+ \rightarrow$ inhibition of TCA cycle.

Inhibitors of Citric Acid Cycle

- a) **Fluoroacetate** inhibits activity of aconitase. In the body, it is converted to fluoroacetyl-CoA, which gives rise to fluorocitrate after condensing with oxaloacetate. The aconitase is inhibited by fluocitrate.
- b) α -ketoglutarate dehydrogenase is inhibited by **arsenic** compounds. Arsenite forms a stable complex with the thiol groups of lipoic acid making it unavailable for the enzyme action.

Thanks

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Oxidation of extra mitochondrial $\text{NADH} + \text{H}^+$

1. Glycerophosphate shuttle
2. Malate-aspartate shuttle

Oxidation of extra mitochondrial $\text{NADH} + \text{H}^+$

- **Cytosolic $\text{NADH} + \text{H}^+$ Challenge:**
- It cannot directly cross the highly selective inner mitochondrial membrane.

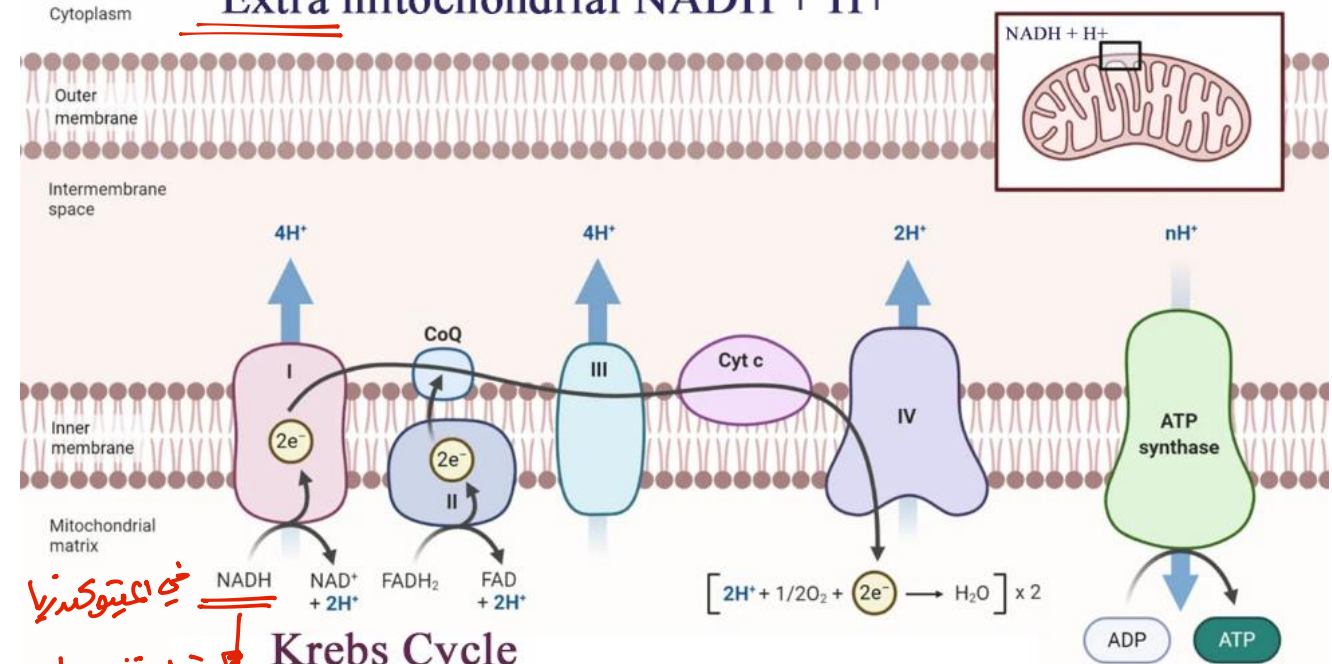
بسبب حجمه وبسبب الـ polarity تعجز

مشكلته انه ما يقدر يدخل جوا الميتوكوندريا
ويقلل diffusion :: لازم وجود shuttle
حتى تستطع الالكترونات ان تدخل الميتوكوندريا

لا يتم تصديره من خلايه
cytosol في الـ
↑ خارج الميتوكوندريا

Glycolysis

Extra mitochondrial $\text{NADH} + \text{H}^+$



في الميتوكوندريا

Krebs Cycle

يتم استخدام حصة الكربس و ETC حتى يتم انتاج الطاقة منه

NADH cannot pass into mitochondria

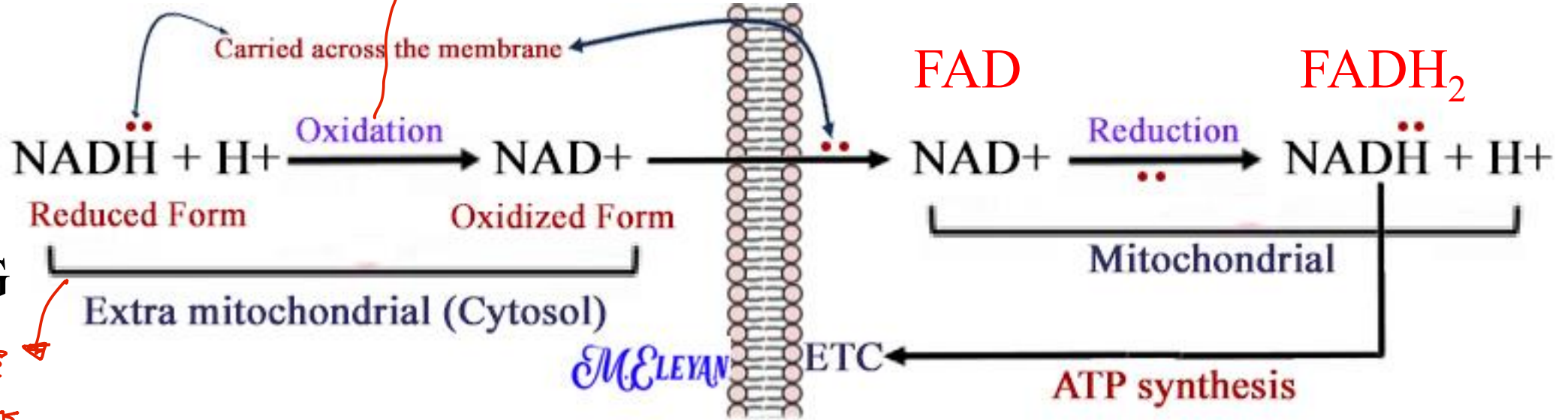
في حالة aerobic يباع يصير oxidation لـ NADH إلى NAD^+ واستترونتهم نقلهم عبر shuttle إلى داخل الميتوكوندريا حتى أستفيد منهم وأحصلهم على NAD^+ مرة ثانية داخل الميتوكوندريا وأعلى reduction وأحولهم $NADH+H^+$ وفي shuttle ثانيي بملهم على FAD ونجبر $FADH_2$ بصلها بخلوا في عاليه تصنيح الـ ATP بواسطة ETC

بجل حبله حتى تستمر على glycolysis وأحصل على الـ NAD^+

جليسرأ لاصيد
3-عوضات

G-3-P

1,3-BPG



- Electrons from NADH are carried across mitochondrial membrane
- NAD^+ must be regenerated for glycolysis and other metabolic processes to continue, so NADH must be oxidized NAD^+
- Don't forget pyruvate to lactate

Oxidation of extra mitochondrial $\text{NADH} + \text{H}^+$

- **The Solution: Shuttles:** To overcome this barrier and utilize $\text{NADH} + \text{H}^+$ for energy production, cells employ special "shuttle systems." These shuttles act as **mediators**, transferring the electrons from cytosolic $\text{NADH} + \text{H}^+$ into the mitochondria.

يقوم الناقلون بالشuttle بحمل الإلكترونات من $\text{NADH} + \text{H}^+$ في السيتوبلازم إلى الميتوكوندريا.

1. Glycerophosphate shuttle
2. Malate-aspartate shuttle

Glycerophosphate Shuttle

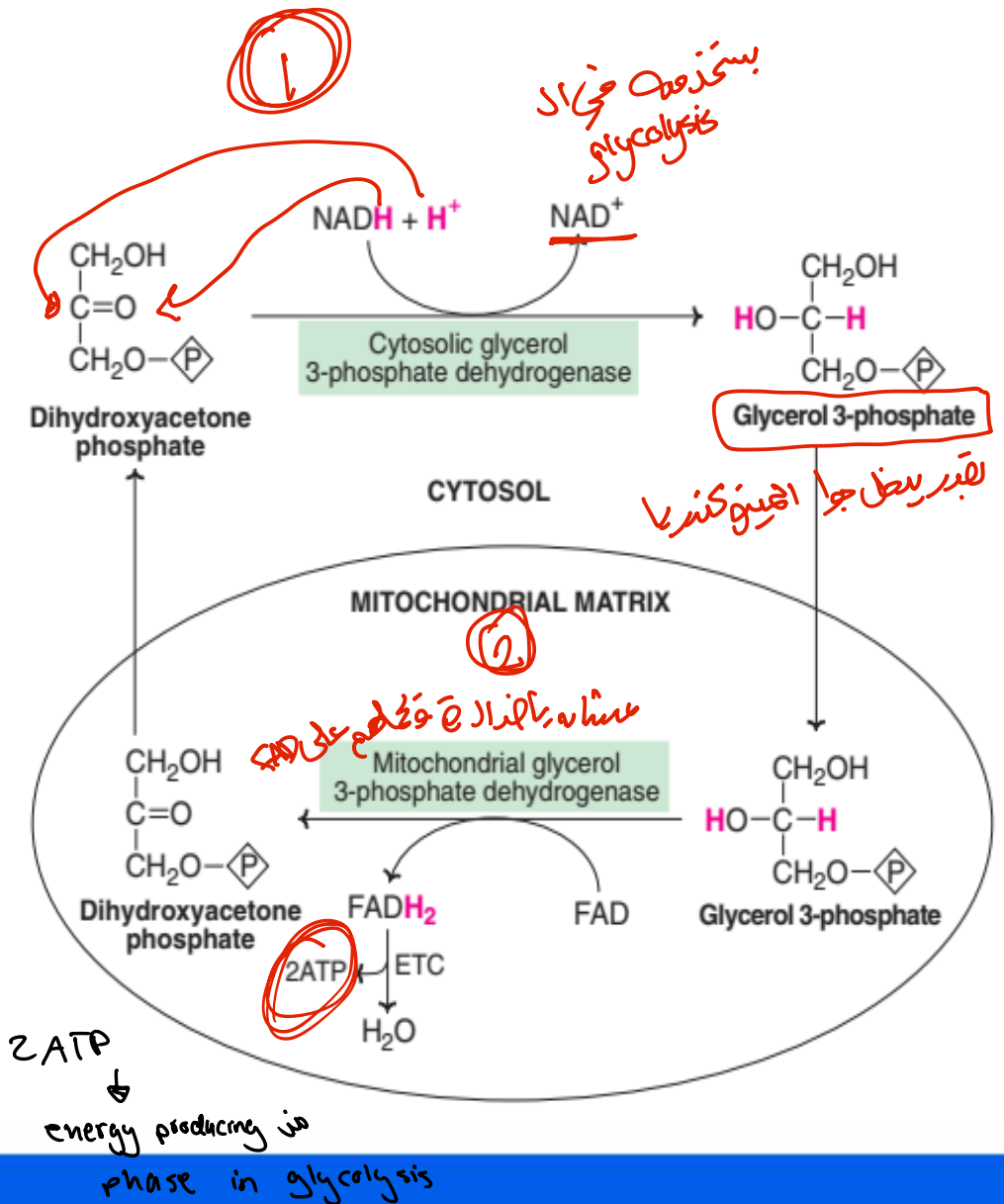
Site
└───┘

- It is important for muscles and nerve cells.
- Mechanism:
 - **Cytoplasmic glycerol-3-phosphate dehydrogenase (GPDH)** uses **NAD⁺** as its coenzyme in the cytosol.
 - **Mitochondrial glycerol-3-phosphate dehydrogenase** utilizes **FAD** as its coenzyme within the mitochondrial inner membrane.

من 2 molecule في 2 molecule من NADH من 2 pyruvate

- The final energy produced is $2 \times 2 \text{ ATP} \rightarrow 4 \text{ ATP} + 2 \text{ ATP}$

ATP = 6
بمجموع هذه الطاقة لاكتمال glycolysis

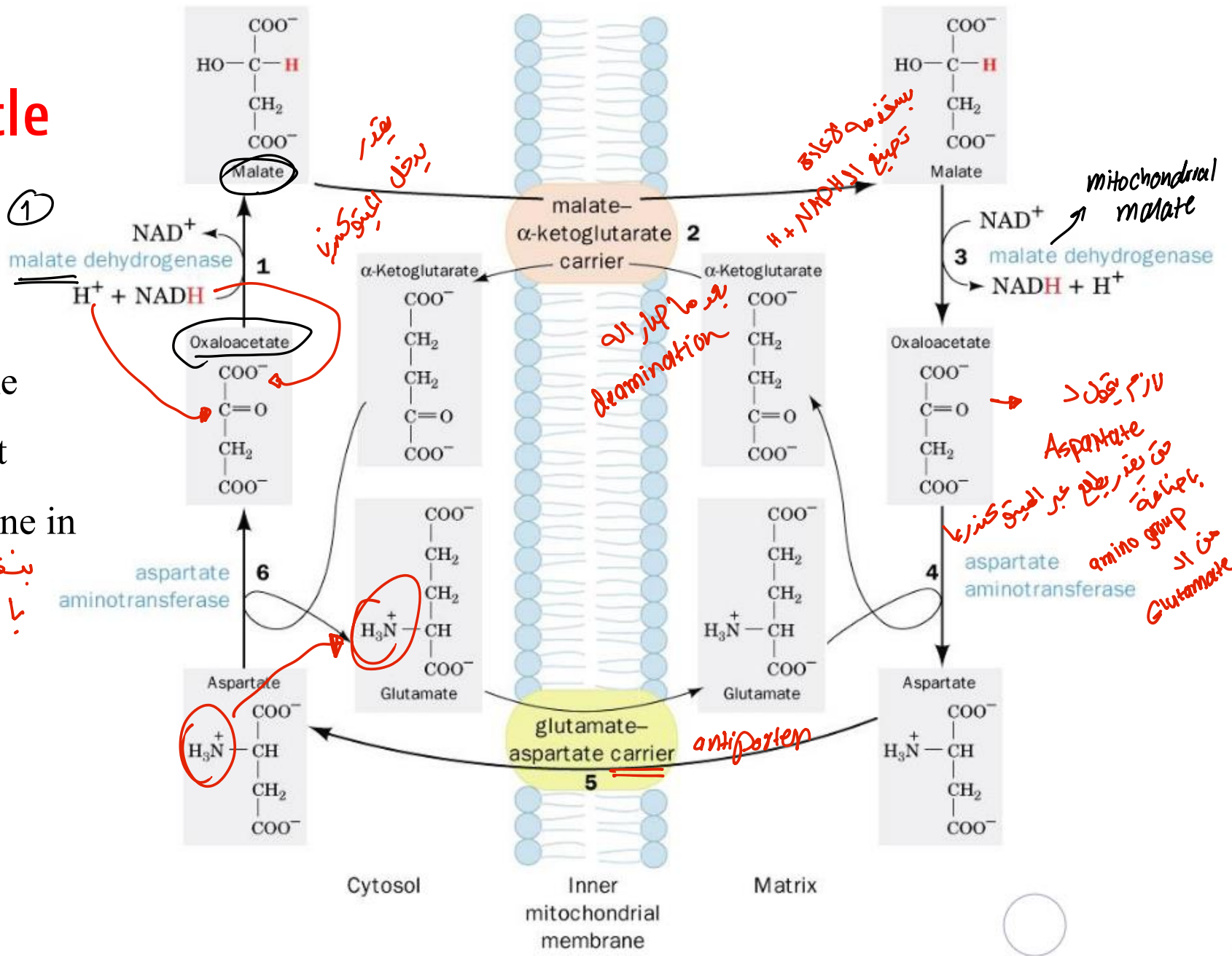


energy producing in phase in glycolysis

Malate - Aspartate Shuttle

- An **carrier** is a type of membrane protein that transports two different molecules or ions across a membrane in opposite directions.

1. Malate-α-ketoglutarate antiporter.
2. Glutamate-aspartate antiporter.



Malate - Aspartate Shuttle

site

- It is important especially in tissues like the liver cells and cardiac muscle cells
- The primary enzyme in this shuttle is malate dehydrogenase (mitochondrial malate dehydrogenase and cytosolic malate dehydrogenase).
- The coenzyme involvement (NAD^+) for both enzymes

• Energy Yield is $2 \times 3 \text{ ATP} \rightarrow 6 \text{ ATP}$ $+ 2 \text{ ATP}$
 $\downarrow$
2 pyruvate
 $\underbrace{\hspace{10em}}_{8 \text{ ATP}}$



Thanks

Presentation by Mohammed Eleyan

Essential Electron Carriers for Energy Production

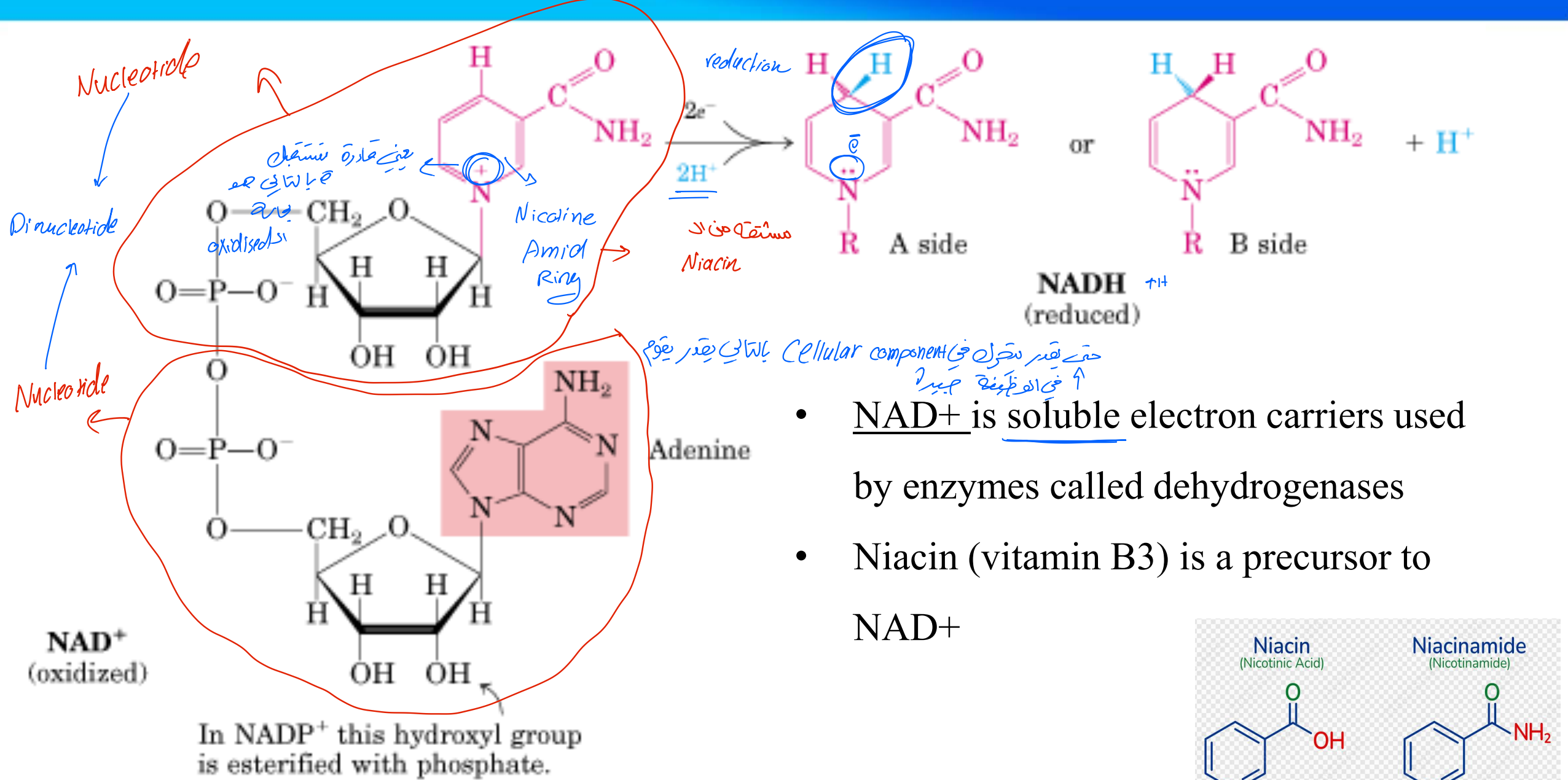
July - 2024

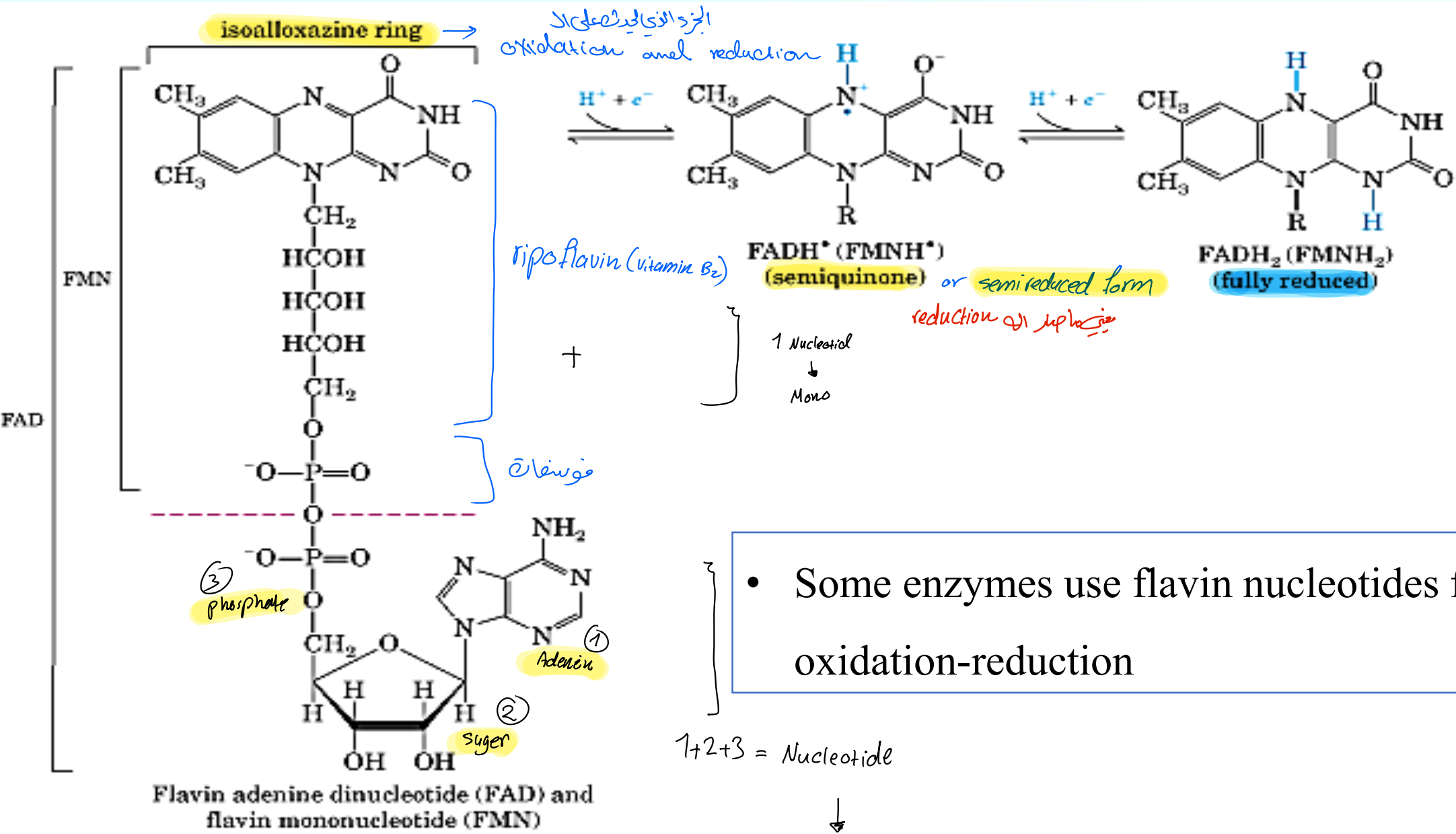
Essential Electron Carriers for Energy Production

- Essential electron carriers are molecules capable of accepting and donating electrons in biological redox reactions, facilitating energy transfer and ultimately ATP production

Essential Electron Carriers for Energy Production

1. NAD⁺: nicotinamide adenine dinucleotide soluble molecule used by dehydrogenases
(non-protein component) → (ليس a.a) تامة مرتبطة بالإنزيم كـ covalent bond
2. FAD: Flavin Adenine Dinucleotide acts as a prosthetic group in flavoproteins.
3. FMN: Flavin Mononucleotide also acting as a prosthetic group in flavoproteins.
4. Ubiquinone also known as coenzyme Q lipid-soluble molecule with isoprenoid chain
5. Cytochromes – proteins that contain a heme prosthetic group
6. Iron-sulfur proteins – Contain iron-sulfur clusters for electron transfer





• Some enzymes use flavin nucleotides for oxidation-reduction

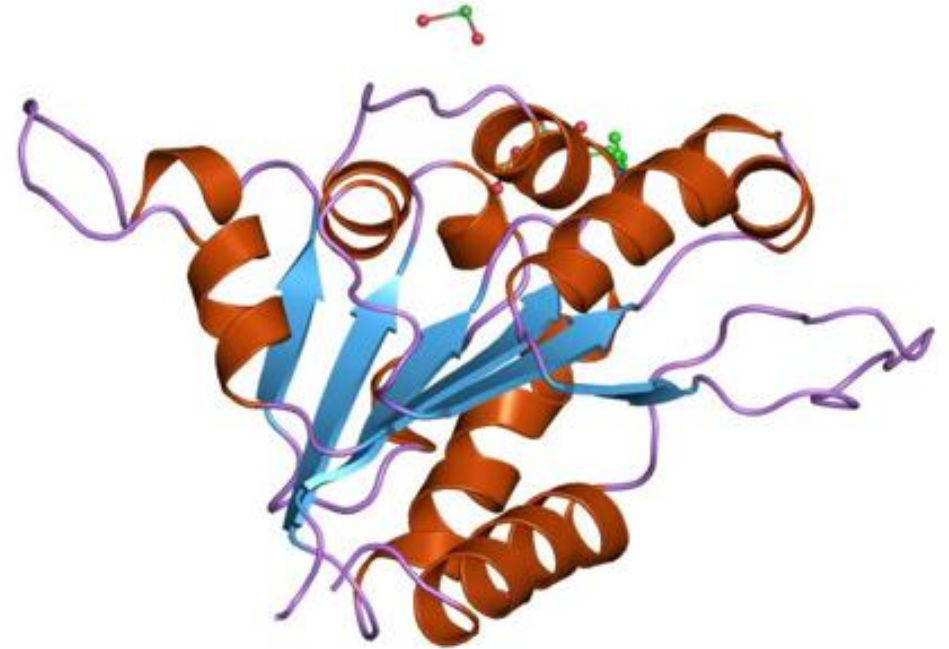
1+2+3 = Nucleotide

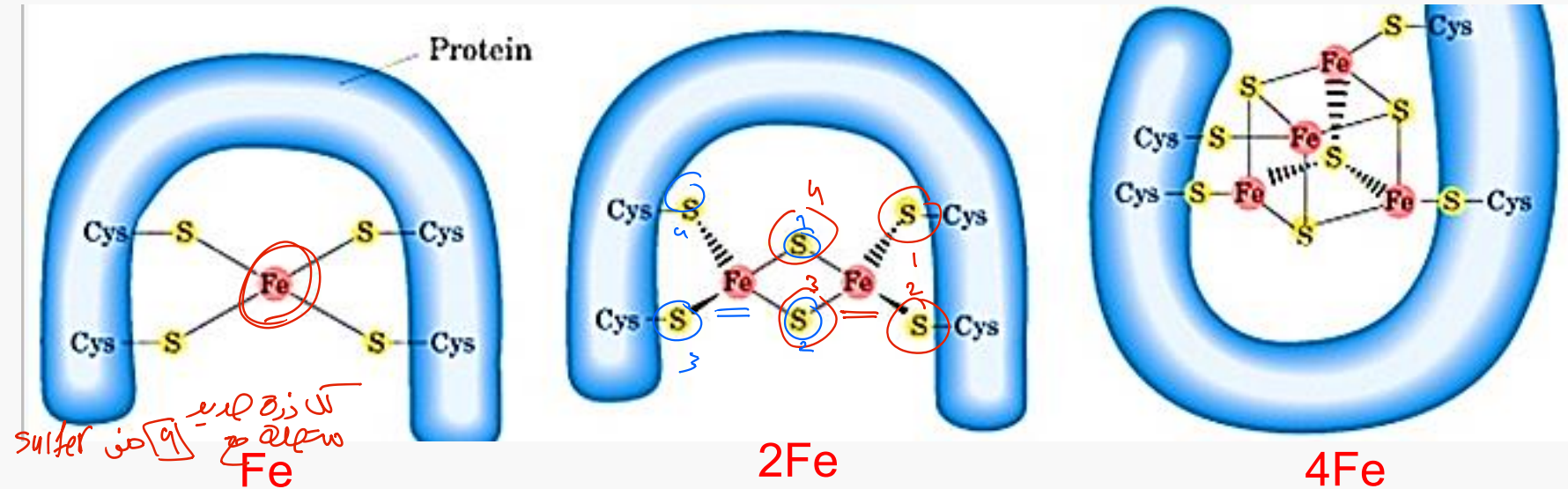
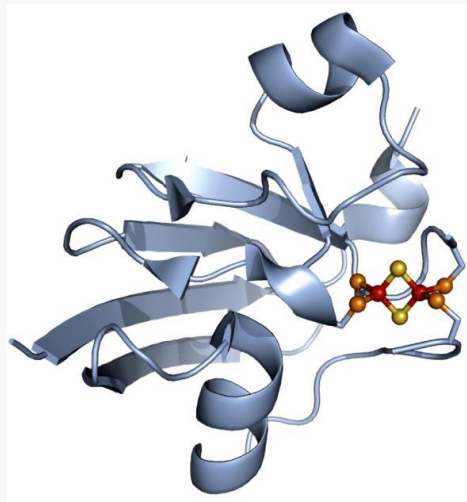
↓

1 Nucleotide + 1 Nucleotide
= dinucleotide

Flavoprotein

- Flavoproteins are a class of enzymes that contain a flavin coenzyme, either FMN or FAD, tightly bound to the protein structure.
- Flavoproteins are capable of accepting or donating one or two electrons.
- Example: succinate dehydrogenase.





Iron-sulfur (Fe-S) centers

حراكي يتكونه جز من البروتين ولها القدرة على منح وقبض الإلكترونات

Iron-sulfur clusters occur in many biological systems, often as components of electron transfer proteins.

Fe atom coordinated to sulfur atoms of Cys residues in the proteins. Each Fe is surrounded by four sulfurs.

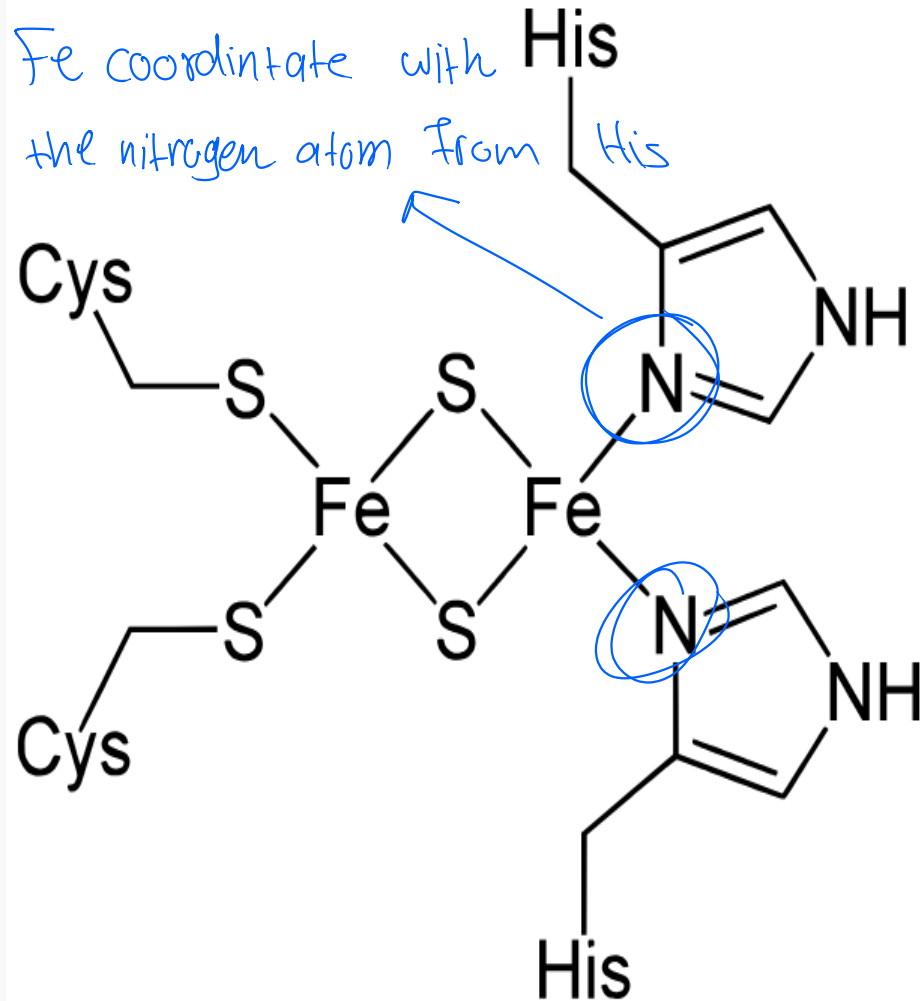
Cysteine

The Fe atom is oxidized or reduced

Iron-sulfur (Fe-S) centers

The iron-sulfur (Fe-S) centers range from simple structures with a single Fe atom coordinated to four Cys groups to more complex Fe-S centers with two or four Fe atoms.

Rieske iron-sulfur center (named John S. Rieske) are a variation on this theme, in which one Fe atom is coordinated to two His residues rather than two Cys residues.



His + histidine

Ubiquinone (coenzyme Q, or simply Q). Lipid-soluble molecule with a long isoprenoid side chain. ← لونه طوي على
Diffusible in the membrane.

Can accept one electron to become coenzyme QH• or ubisemiquinone (semiquinone or radical form).

↳ active molecule contain one free electron

Can accept two electrons to become ubiquinol.

coenzyme QH₂. (fully reduced form)

OR

(Hydroquinone form)

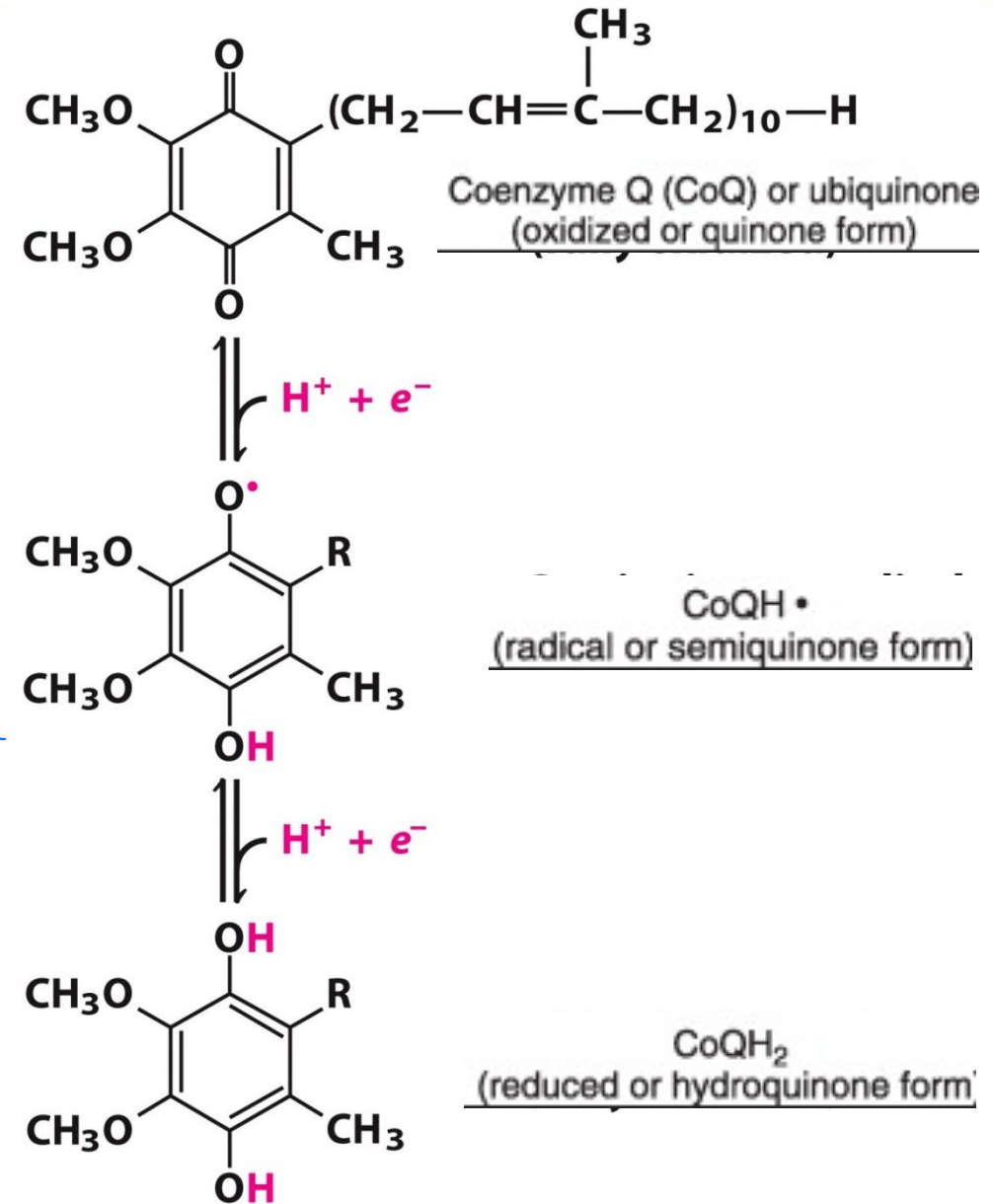
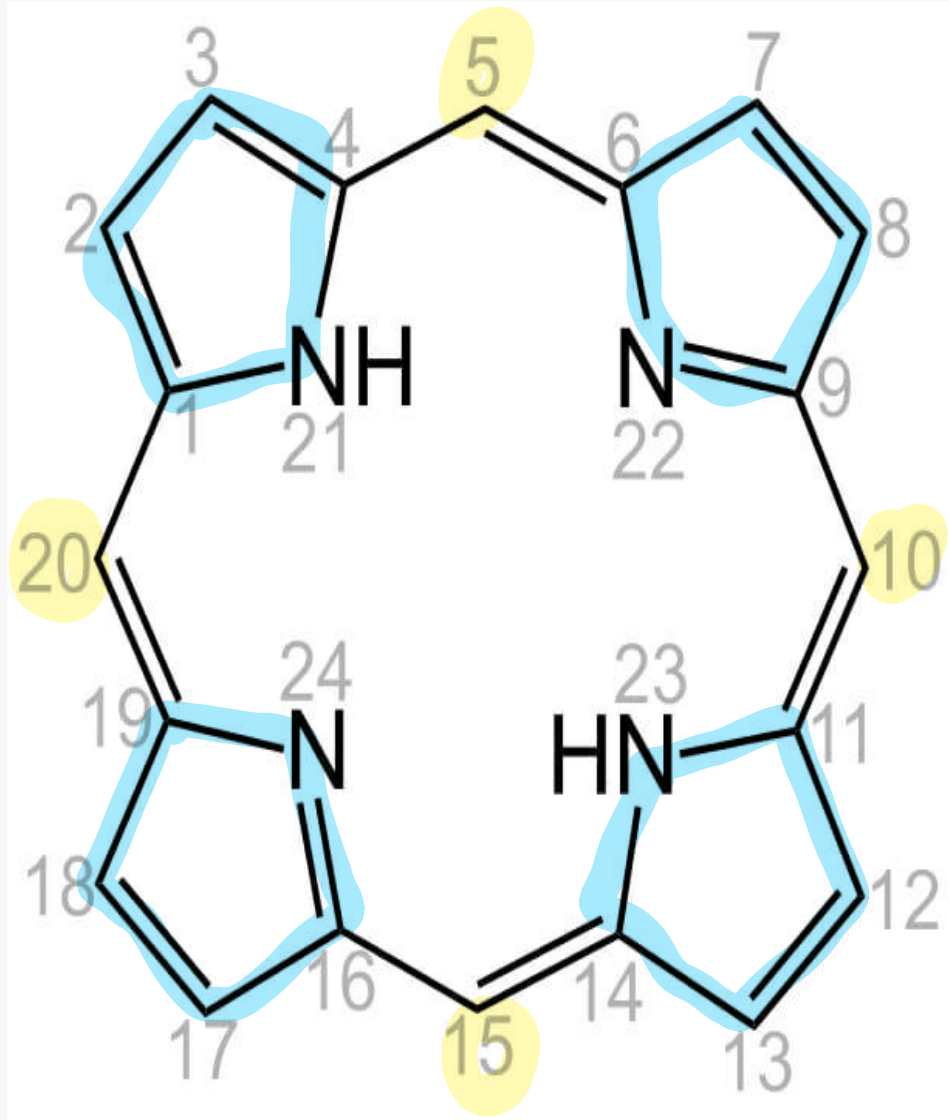


Figure 19-3
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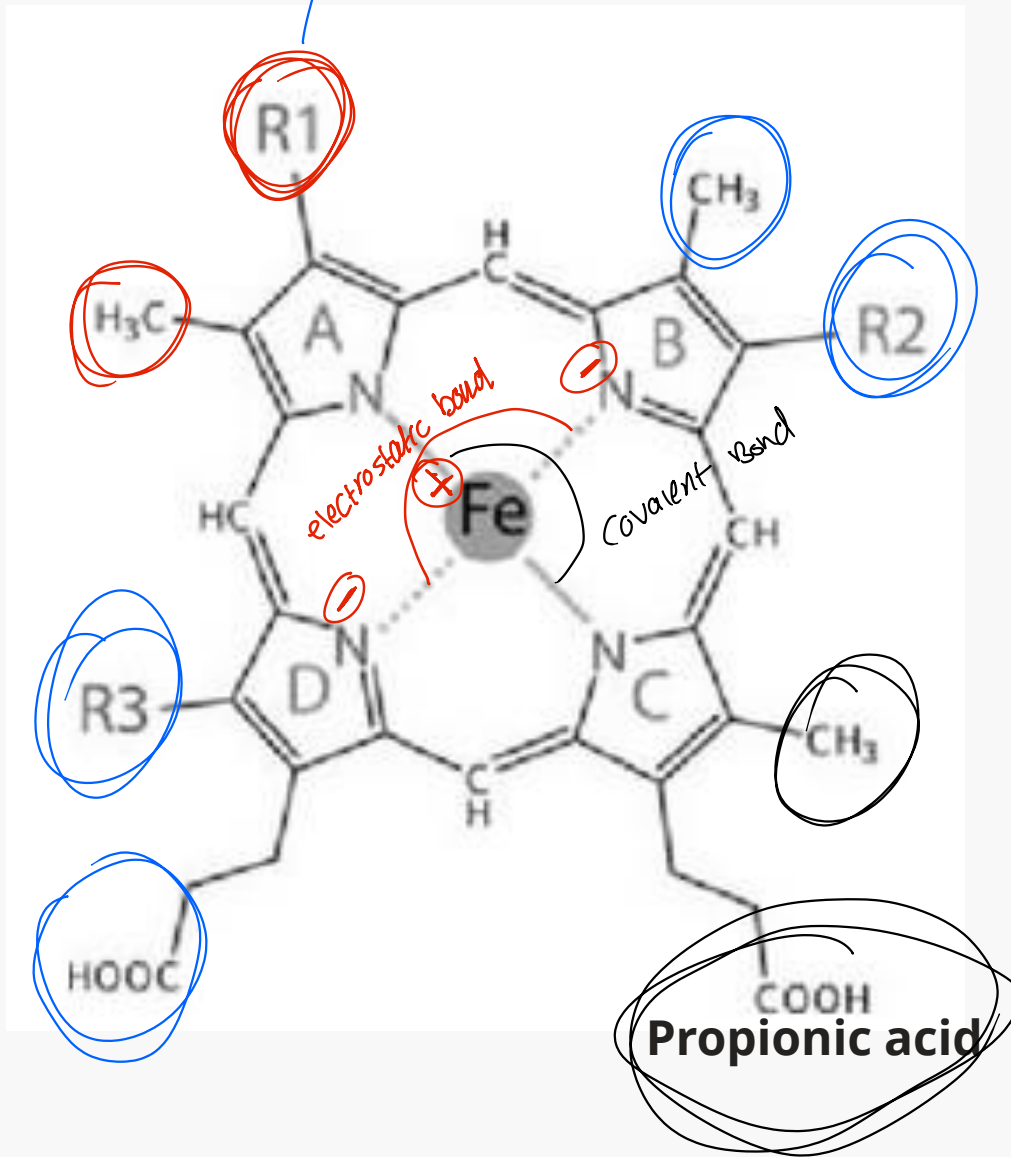
Cytochromes are proteins that contain heme prosthetic groups

Heme is a metalloporphyrin (porphyrin + Fe ion)

Porphyrin is a cyclic structure consists of four pyrrole rings (five-membered, nitrogen containing rings) linked by four bridging carbon atoms



هذه هي جزيئات Heme
التي تحتوي على حديد



Cytochromes are proteins that contain heme prosthetic groups

The four nitrogen atoms are coordinated with a central Fe ion, either Fe^{2+} or Fe^{3+} . *ferric*
ferrus

All heme derivatives have the same basic structure formed of a cyclic tetrapyrrole found in a b-type heme (or protoporphyrin IX). The four rings of the porphyrin macrocycle and the different substitutions at various side chains are indicated as A, B, C and D and R1, R and R3, respectively. The different chemical moieties occupying the R1, R and R3 positions of different hemes are listed in the next slide.

Cytochromes are proteins that contain heme prosthetic groups

- Iron protoporphyrin IX is found in b-type cytochromes and in hemoglobin and myoglobin

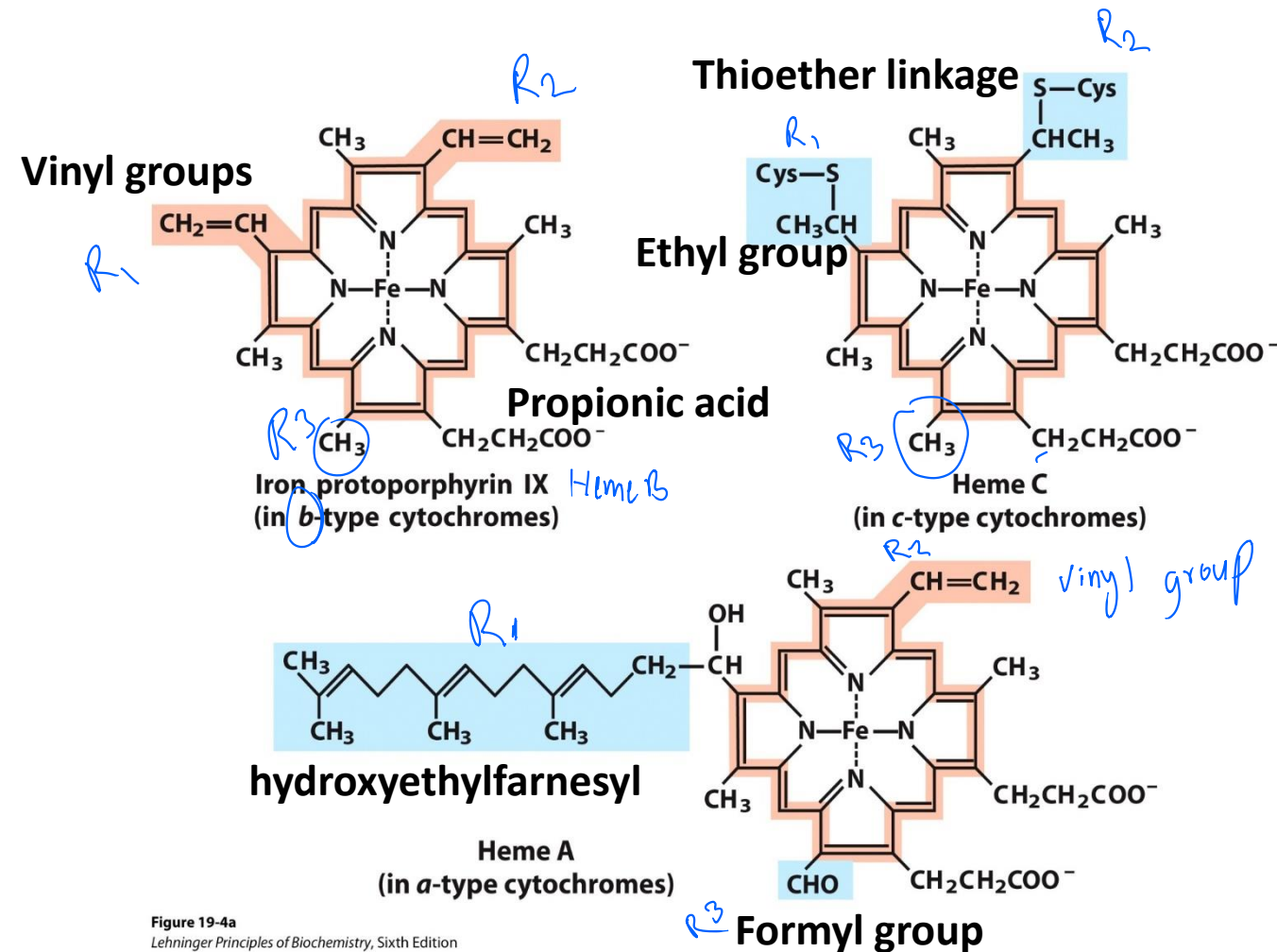
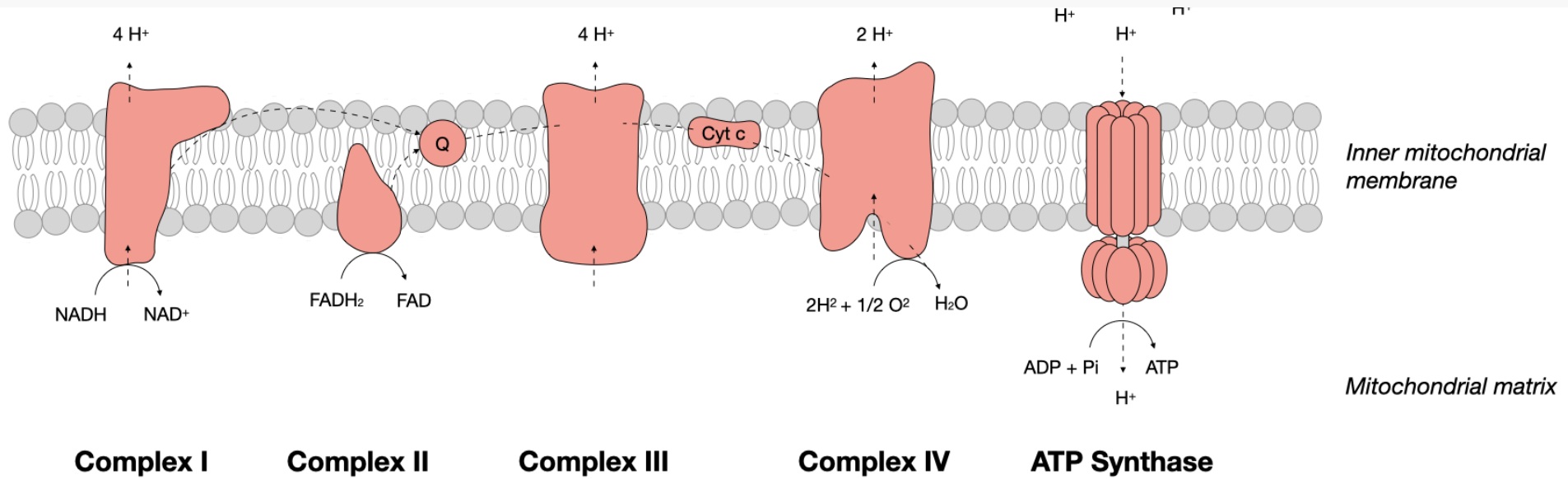


Figure 19-4a
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Presentation by Mohammed Eleyan

Respiratory Chain in Biochemistry

July - 2024



Oxidative Phosphorylation

Oxidative phosphorylation is made up of two closely connected components: the electron transport chain and chemiosmosis.

↓
 ATP ← 1/2 O₂ → H₂O
 (Handwritten note in Arabic script)

- Mitochondria contain two membranes, an outer membrane permeable to small molecules and ions and an impermeable inner membrane.
- The inner membrane contains components of the respiratory chain for transfer of electrons to O_2 .
- The inner membrane also contains ATP synthase, an enzyme that synthesizes ATP.

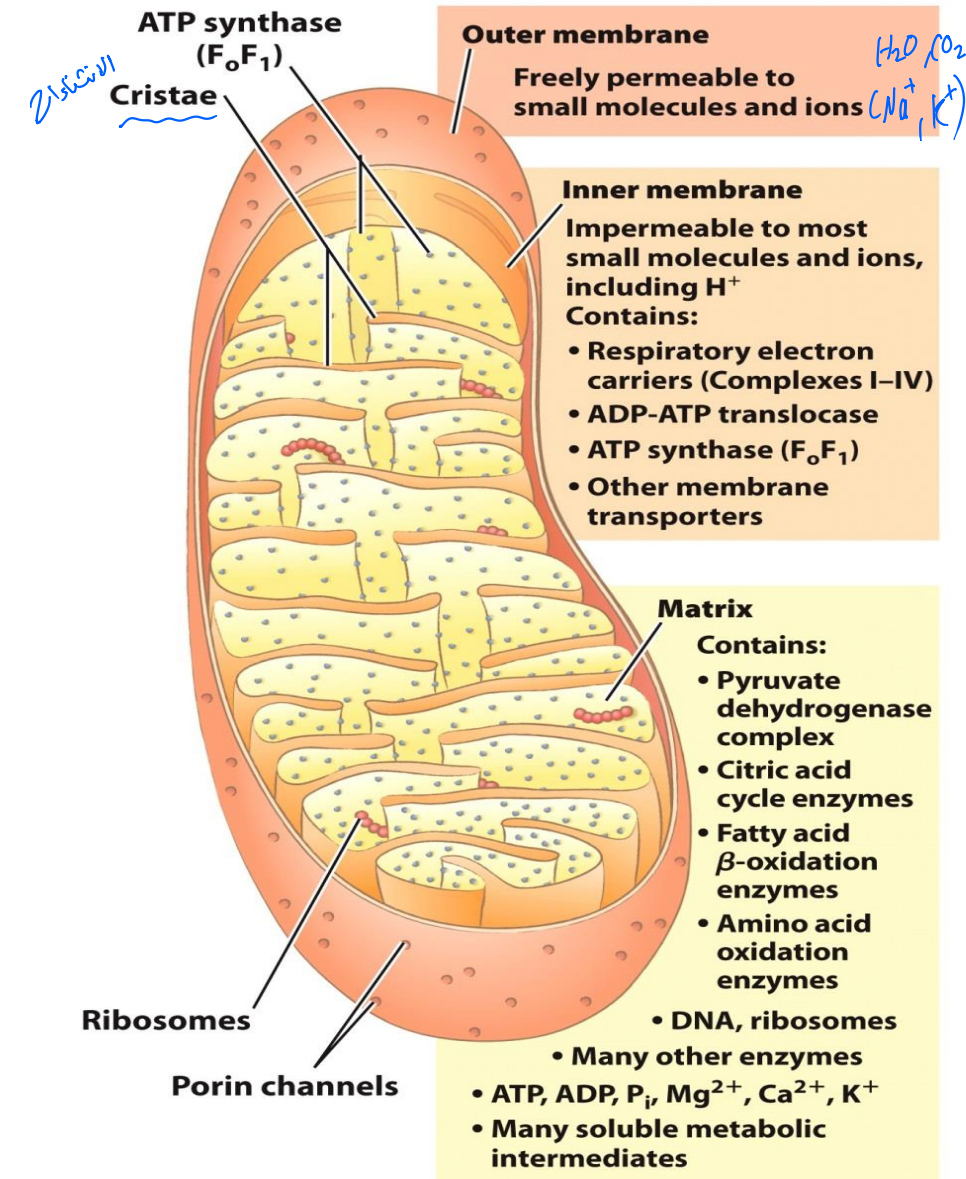
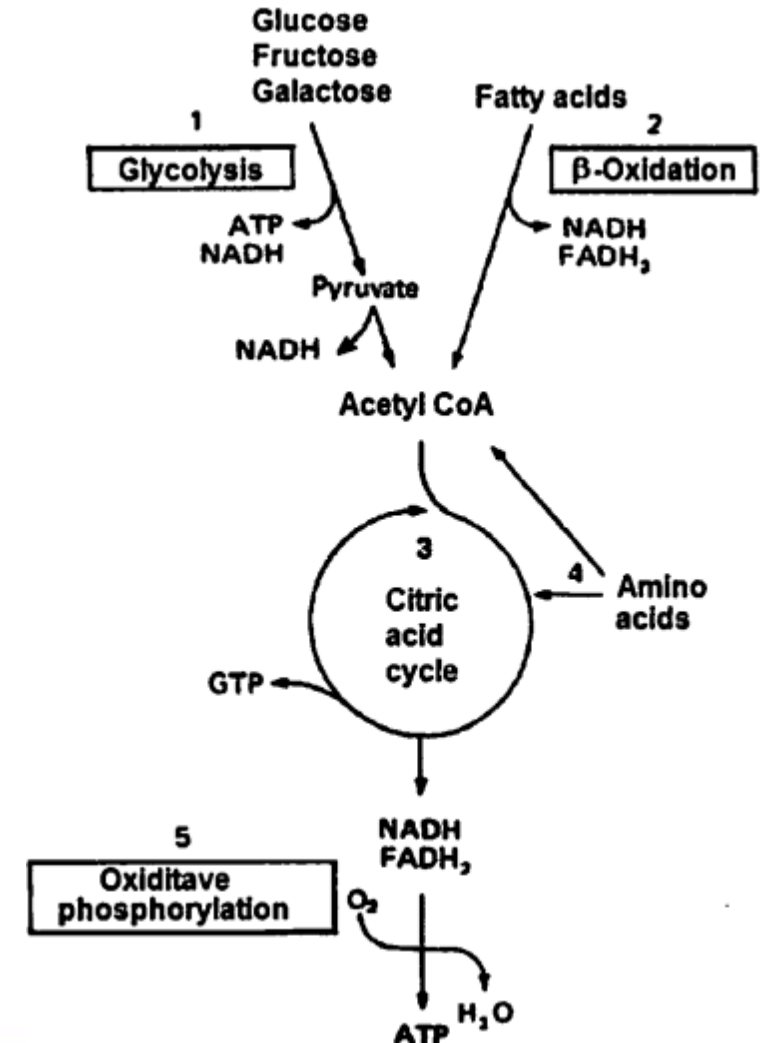


Figure 19-2a
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Electron Transport Chain/Respiratory Chain

- Dehydrogenases produced NADH and FADH_2
- What happens to the electrons stored in NADH and FADH_2 ?
 - They get transferred to O_2 through a series of electron carriers located in the inner membrane of mitochondria.
- Definition: It is the final common pathway in aerobic cells by which electrons derived from various substances (carbohydrate, amino acids and fatty acids) are transferred to oxygen to form water.



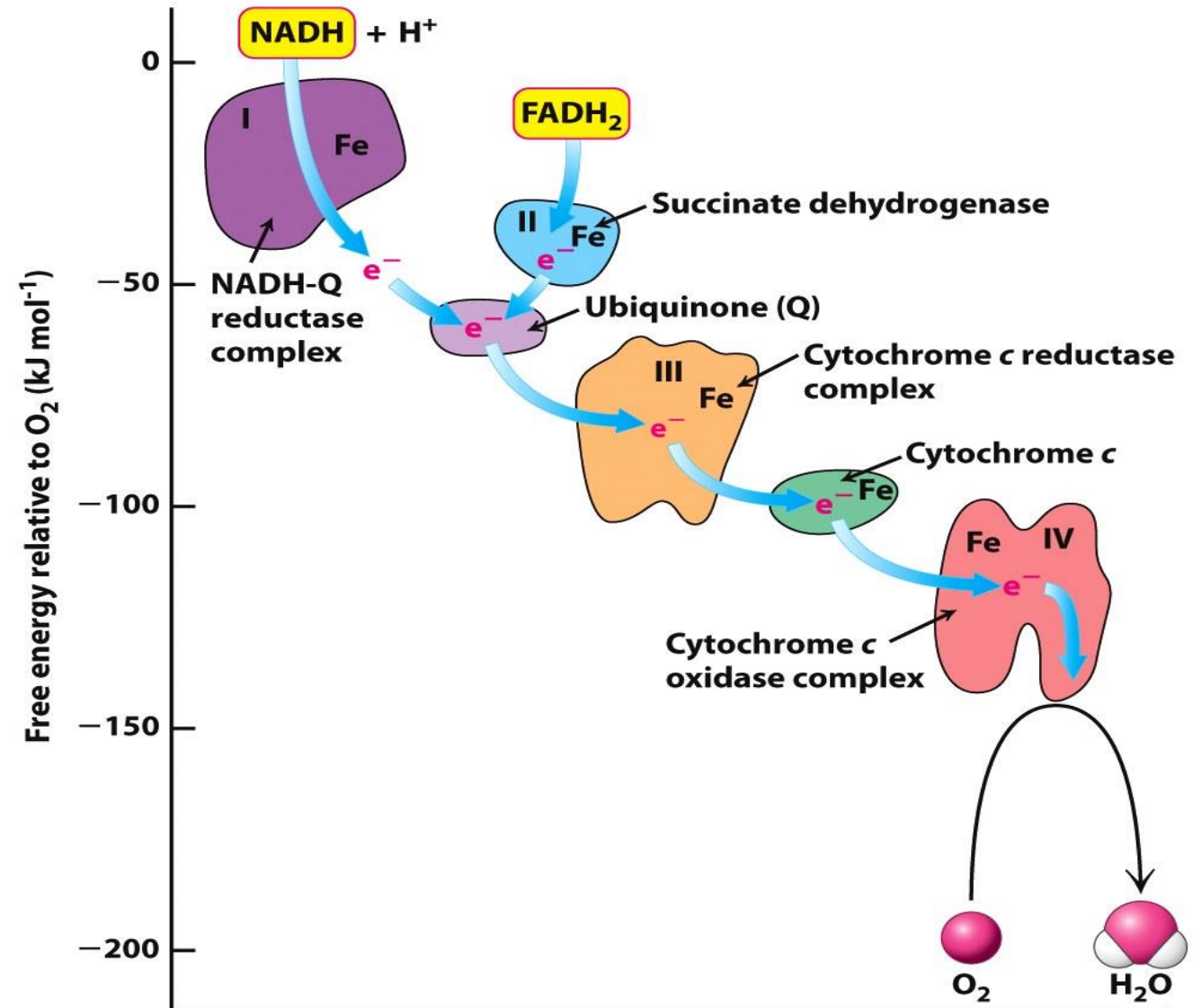
Electron Transport Chain Components

1. Protein complexes:

- I. NADH-Q reductase
- II. Succinate dehydrogenase
- III. Cytochrome C reductase
- IV. Cytochrome C oxidase

2. Bridging components:

Coenzyme Q and Cytochrome C

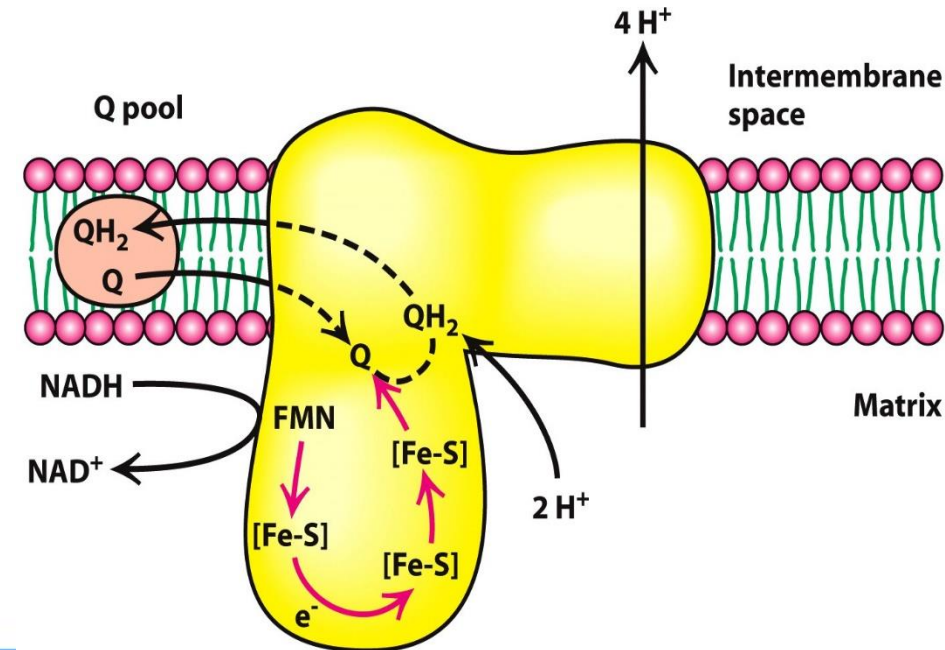


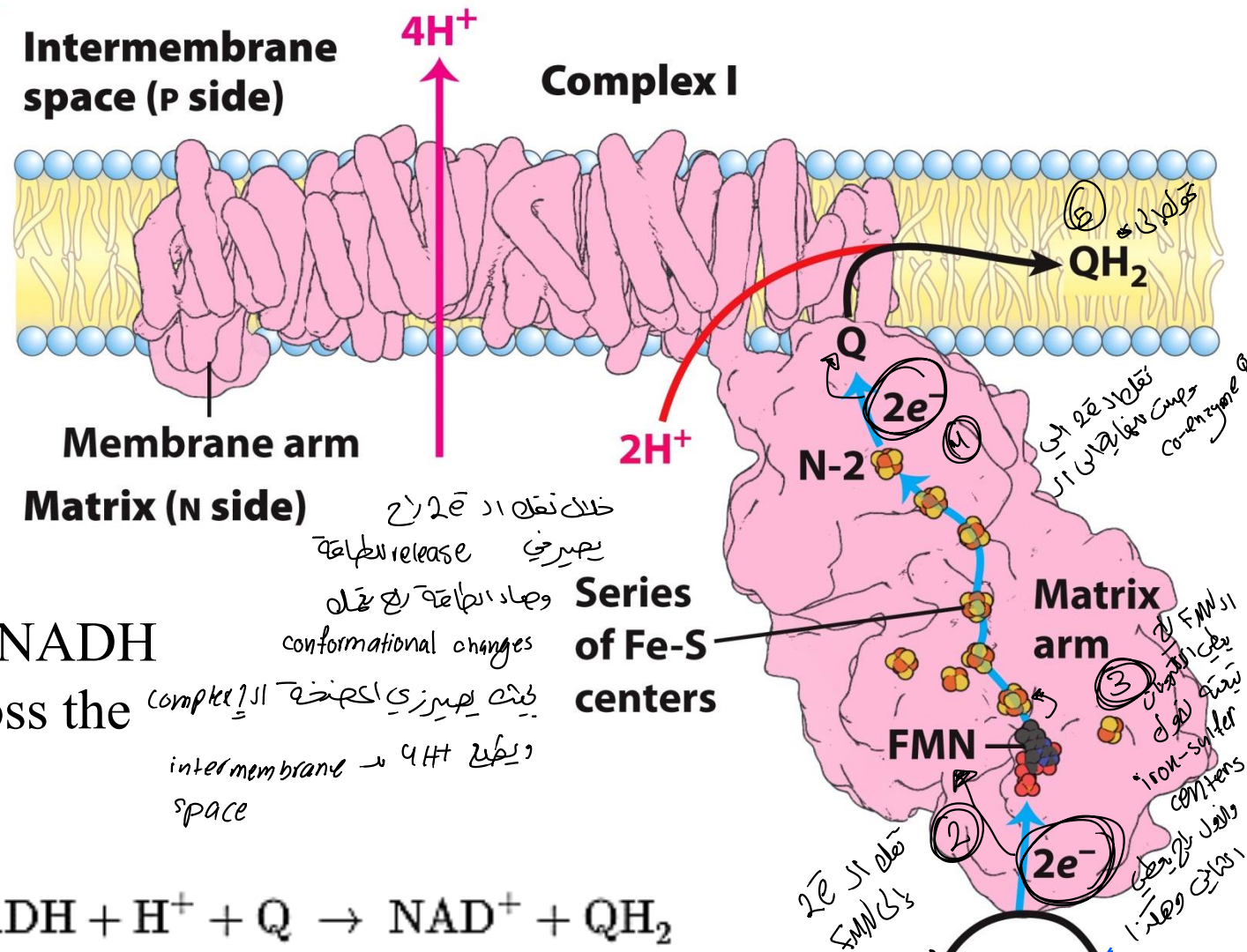
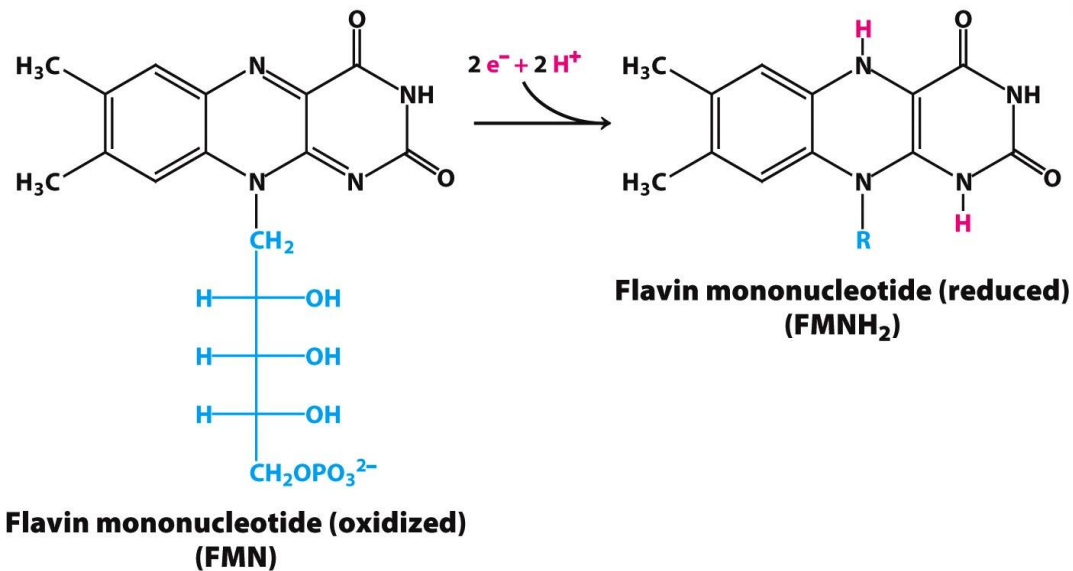
Complex I: NADH to Ubiquinone

oxidation

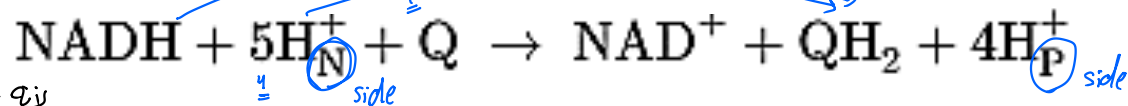
reduction

- Names: Complex I, NADH:ubiquinone oxidoreductase or NADH dehydrogenase.
- Def: It is a large enzyme (flavoprotein), L-shaped, with one arm embedded in the inner membrane and the other extending into the matrix.
- Composition: It is composed of 45 different polypeptide chains, including an:
 1. NADH dehydrogenase
 2. FMN
 3. Iron-sulfur centers.





Complex I transfers the electrons from NADH to ubiquinone and pumps 4 protons across the inner mitochondrial membrane

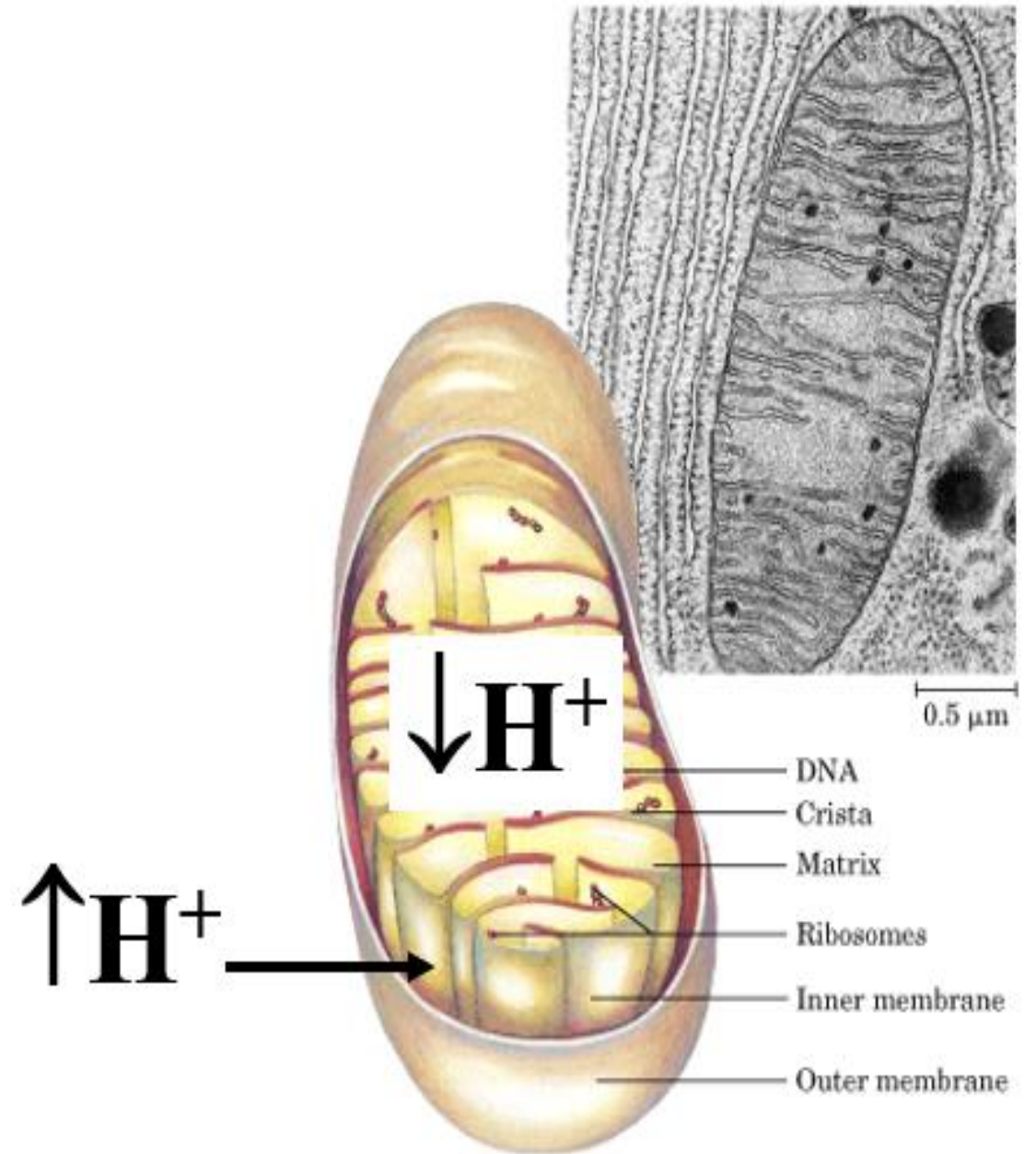


P for the positive side (the intermembrane space), N for the negative side (the matrix)

H^+ are pumped out of the mitochondrial matrix.

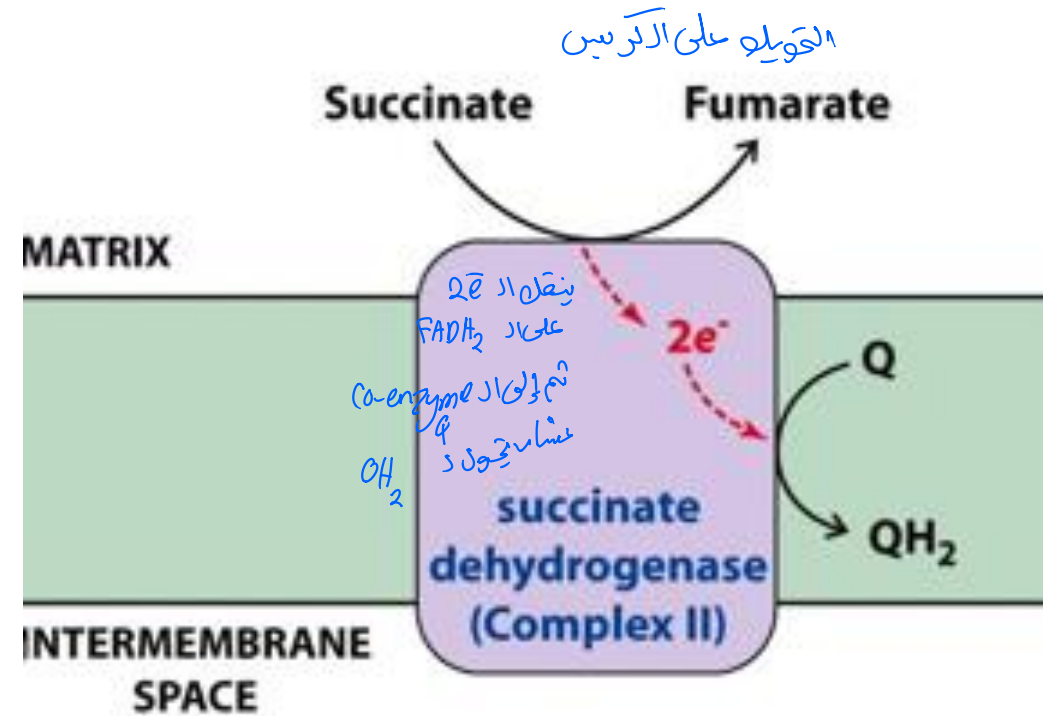
Therefore a H^+ gradient is being built up.

القوة الدافعة
للـ H^+
The matrix becomes negatively charged and the intermembrane space becomes positively charged



Complex II: Succinate to Ubiquinone

- Names: Complex II, succinate-coenzyme Q reductase , succinate dehydrogenase
- Def: the only membrane-bound enzyme in the citric acid cycle and participate in electron transport chain



Complex II: Succinate to Ubiquinone

- Composition
 1. subunits C and D are integral membrane proteins, they contain heme b, and binding site for Q.
 2. Subunits A and B extend into the matrix; they contain Fe-S centers, bound FAD, and a binding site for the substrate, succinate

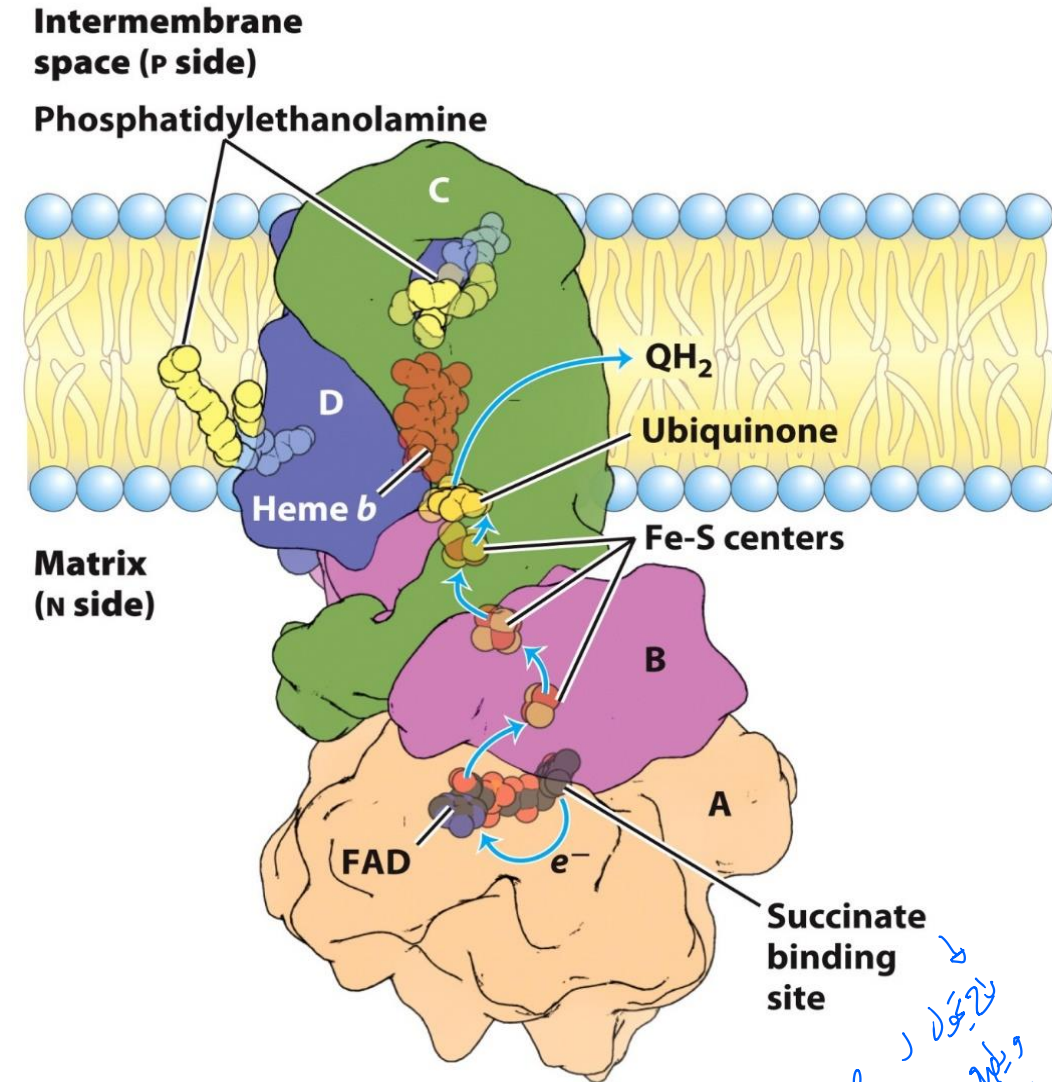


Figure 19-10
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Handwritten notes in blue ink: "Succinate", "FAD", "Ubiquinone", "Ubiquinol", "QH₂", "e⁻", "Matrix", "Intermembrane space", "P side", "N side", "Matrix (N side)", "Intermembrane space (P side)", "Phosphatidylethanolamine", "Heme b", "Fe-S centers", "Succinate binding site", "FAD", "Ubiquinone", "Ubiquinol", "QH₂", "e⁻".

Complex II: Succinate to Ubiquinone

- Electron transfer through Complex II is not accompanied by proton pumping across the inner membrane, although the QH₂ produced by succinate oxidation will be used by Complex III to drive proton transfer.
- The heme b of Complex II is apparently not in the direct path of electron transfer; it serves instead to reduce the frequency with which electrons “leak” out of the system, moving from succinate to molecular oxygen to produce the reactive oxygen species (ROS) hydrogen peroxide (H₂O₂) and the superoxide radical ($\cdot\text{O}_2$),
لے کھاجے ای پروٹین و PNA و لکڑے mutations کثیر و صیایک damage و اظہار کتوت -2),
یعنی ہر وقت QH₂ جے FAD سے اس سے
یعنی ہر وقت اس سے مستقبلہ لے

Complex II: Succinate to Ubiquinone

different subunits
خلاف في الجينات المسؤولة عن تكوينه

free radicals
leakage
تسرب في الجزيئات الحرة

- Some individuals with point mutations in Complex II subunits near heme b or the ubiquinone-binding site suffer from hereditary paraganglioma, characterized by benign tumors of the head and neck, commonly in **the carotid body**, an organ that senses O_2 levels in the blood. These mutations result in greater production of ROS, which cause DNA damage and genome instability that can lead to cancer.

Mutations that affect the succinate-binding region in Complex II may lead to degenerative changes in the central nervous system, and some mutations are associated with tumors of the adrenal medulla.

Complex III of ETC

- Names: cytochrome bc1 complex or CoQH₂-cytochrome c oxidoreductase, cytochrome reductase.
- Transfers electrons from ubiquinol (QH₂) to cytochrome c

oxidation of
reduction of

Complex III of ETC

يعني لو عملت خط بالوسط راح يكون الجزء
اليمين نفس الجزء اليسار

The complex is a dimer of identical monomers, each with 11 different subunits.

يعني كذا دimer فيه 22

The functional core of each monomer consists of three subunits:

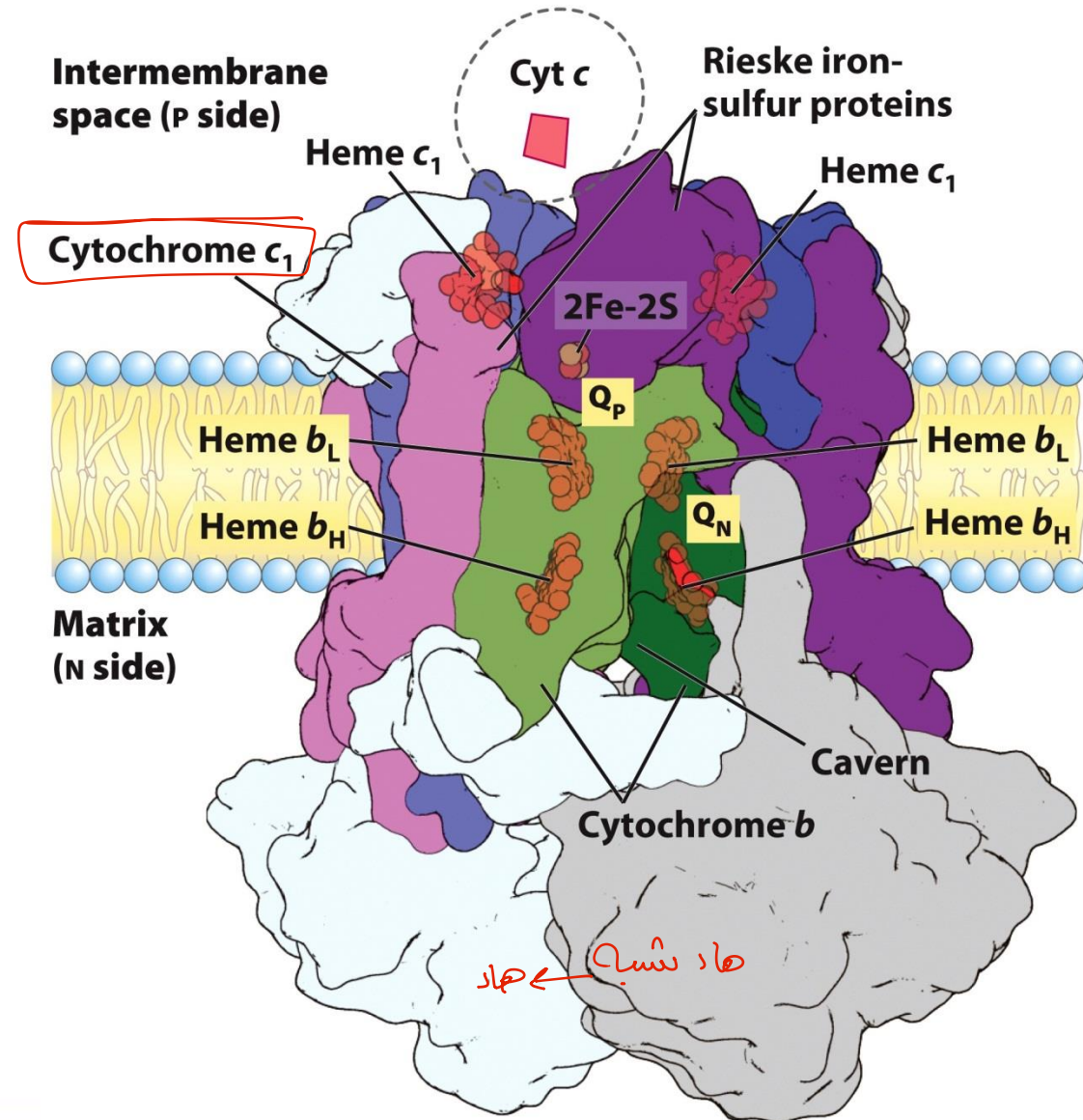
الجزء الوسطي

يتمتعون في انفسهم الفردي

1. cytochrome b [with its two hemes (b_L and b_H)]
2. The Rieske iron-sulfur protein
3. Cytochrome c1 [its heme]

Low redox potential

High redox potential



قار نشبة
قار

Complex III of ETC

Heme b_L (Low potential):

- **Reduction Potential:** Heme b_L has a lower redox potential than heme b_H. This lower potential allows it to facilitate electron transfer earlier in the Q cycle within Complex III.

Heme b_H (High potential):

- **Reduction Potential:** Heme b_H has a higher redox potential compared to heme b_L. This higher potential is necessary for its role in accepting electrons within Complex III.

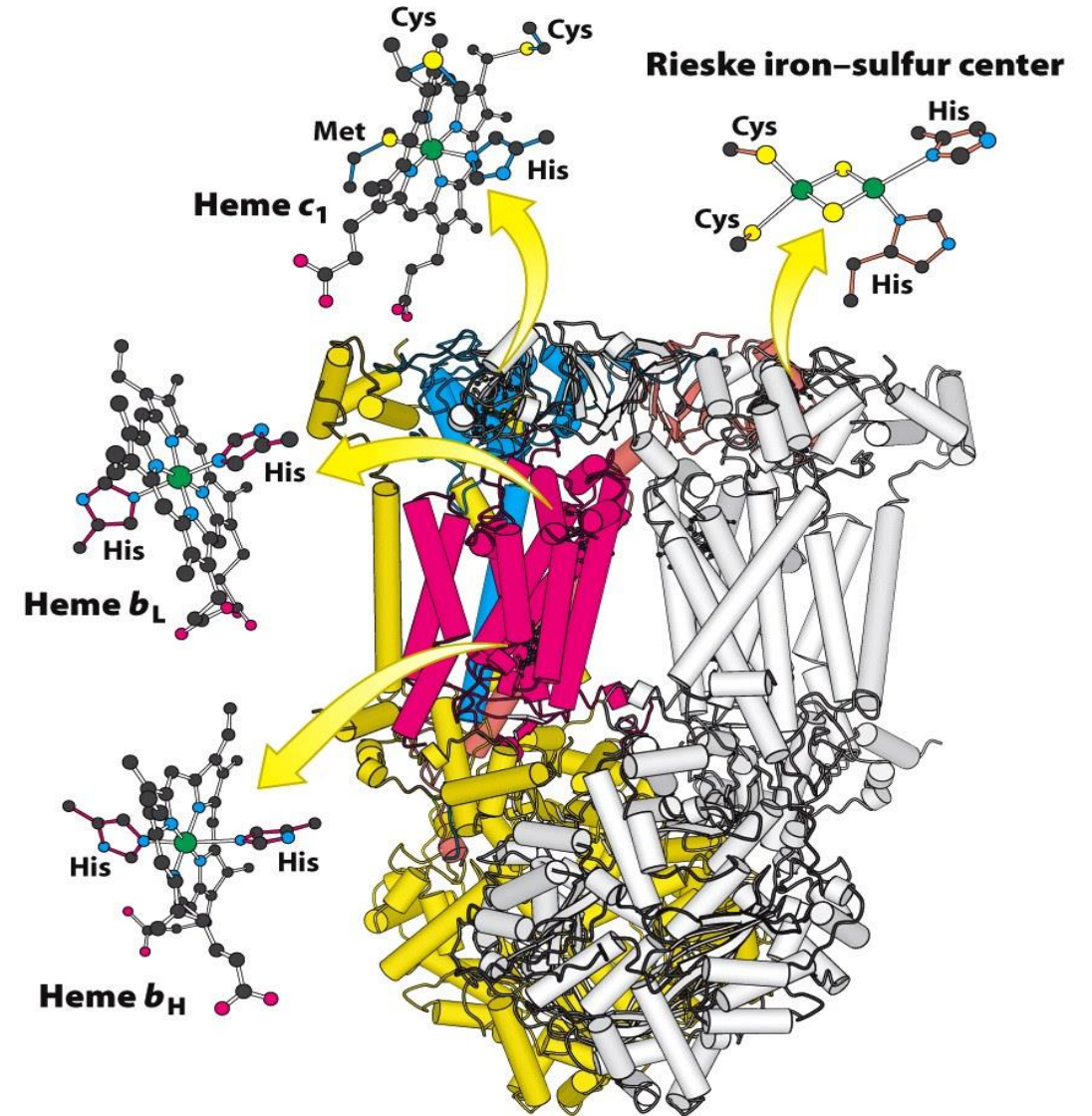
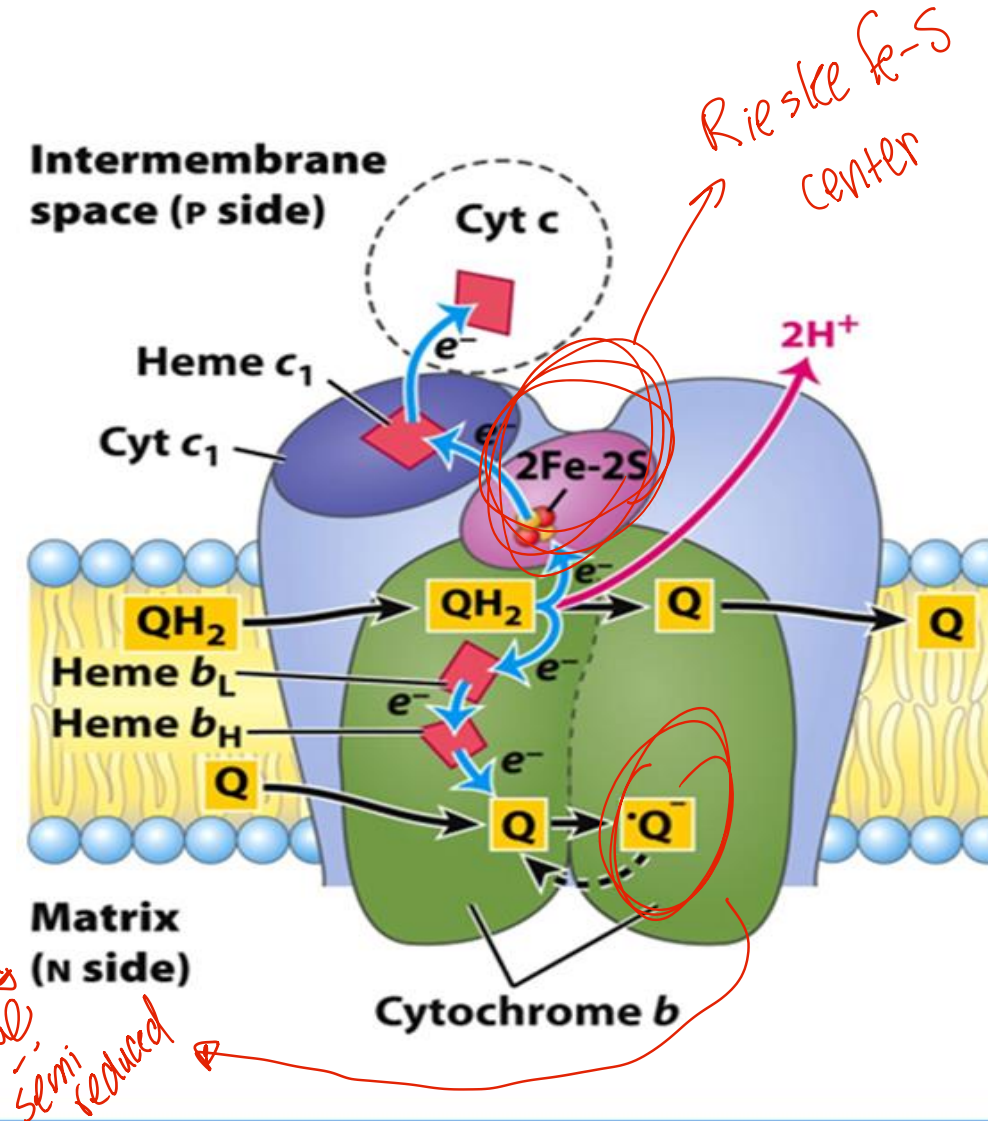


Figure 19.12
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Complex III of ETC

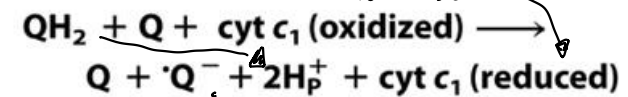
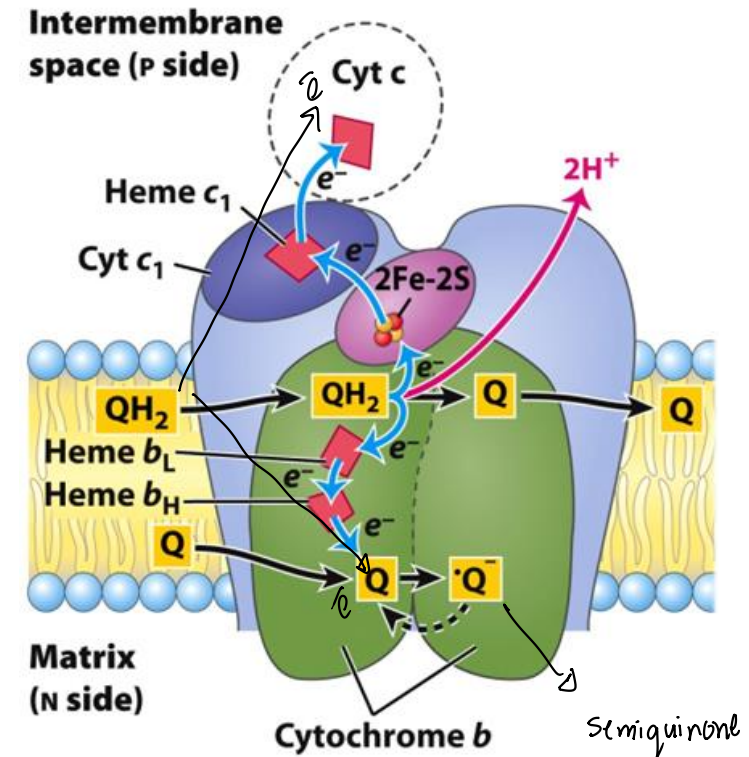
- In the transfer of electrons, coenzyme QH_2 has two electrons to transfer, but cytochrome c molecule can accept 1 electron.
- Each QH_2 donates:
 - one electron (via the Rieske Fe-S center) to cytochrome c_1 then cytochrome c .
 - one electron (via cytochrome b) to a molecule of Q .



The Q Cycle of Complex III

- In the first stage, Q on the N side is reduced to the ubisemiquinone (semiquinone), which moves back into position to accept another electron.

أول مرحلة من دورة Q
حيث يتم اختزال Q في الجانب N إلى
الـ ubisemiquinone (semiquinone)

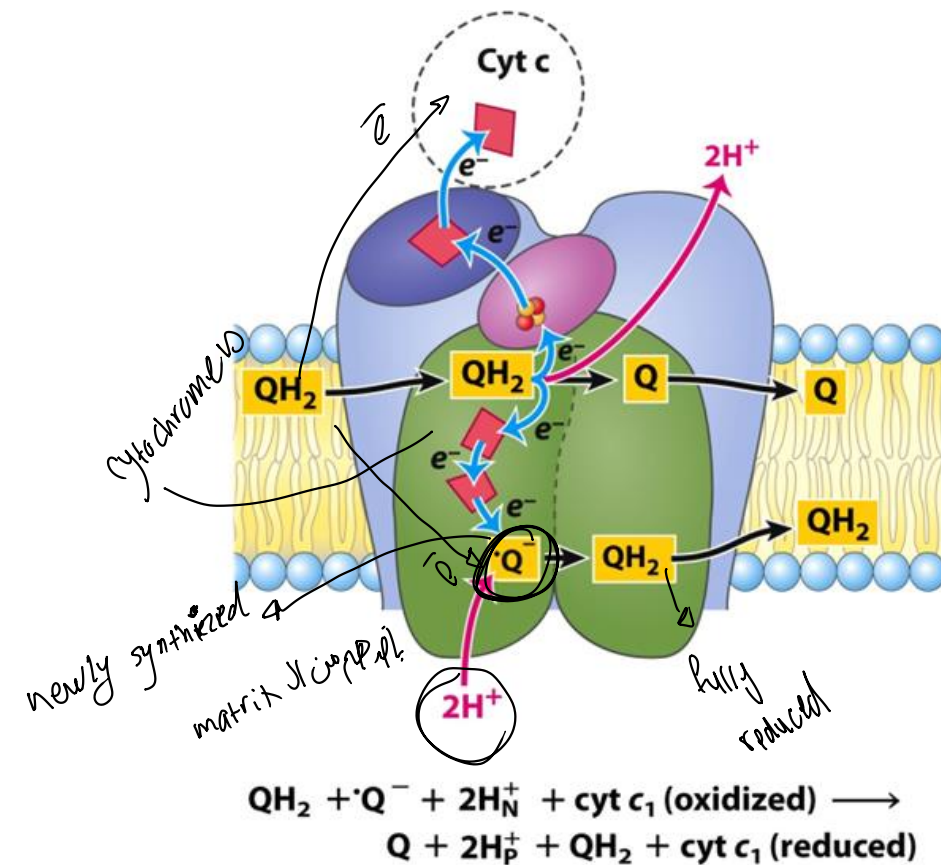


أول مرحلة من دورة Q
حيث يتم اختزال Q في الجانب N إلى
الـ ubisemiquinone (semiquinone)

The Q Cycle of Complex III

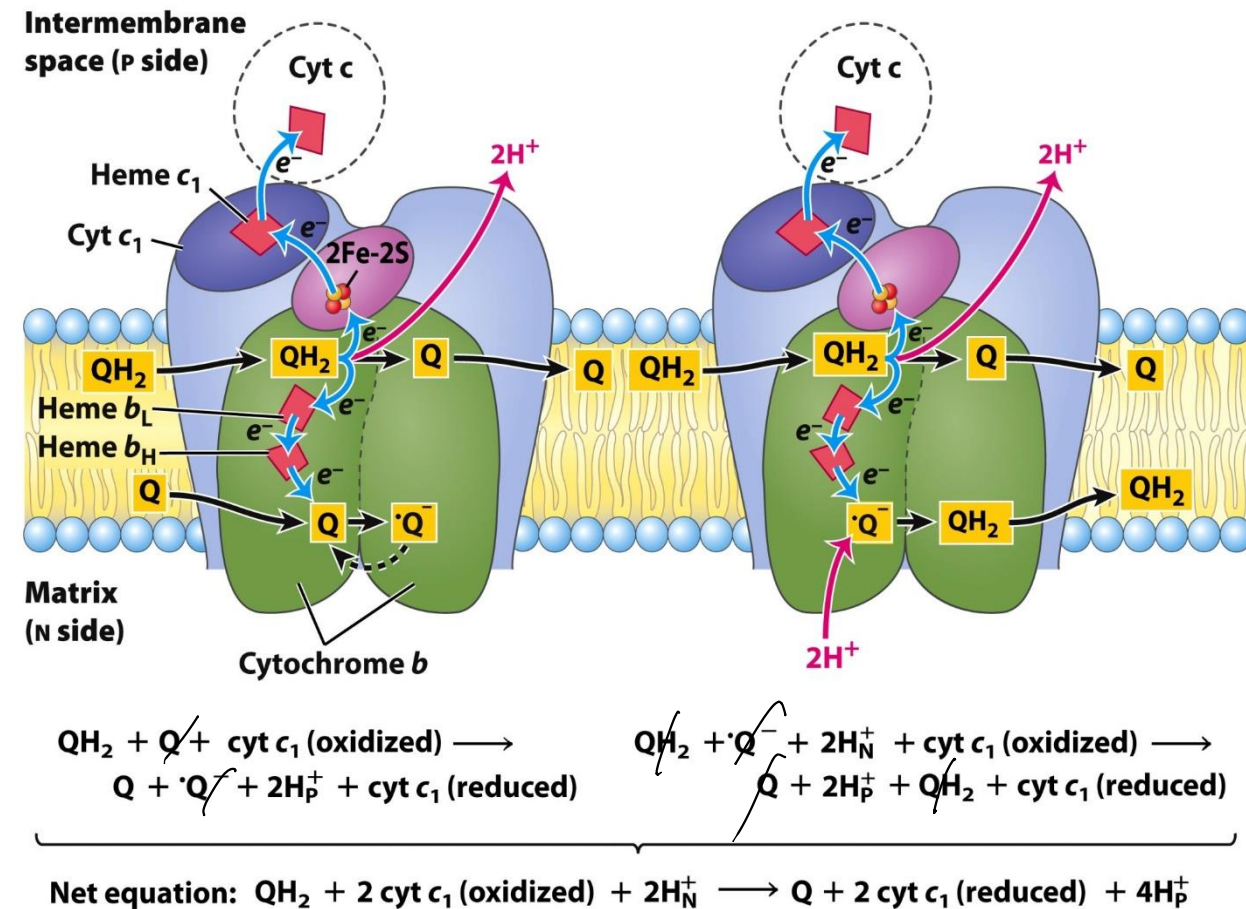
- In the second stage, the semiquinone radical is converted to QH₂.

التي تسمى Pumps
 2H⁺ في المرحلة الثانية
 في المرحلة الأولى 2H⁺



The Q Cycle of Complex III

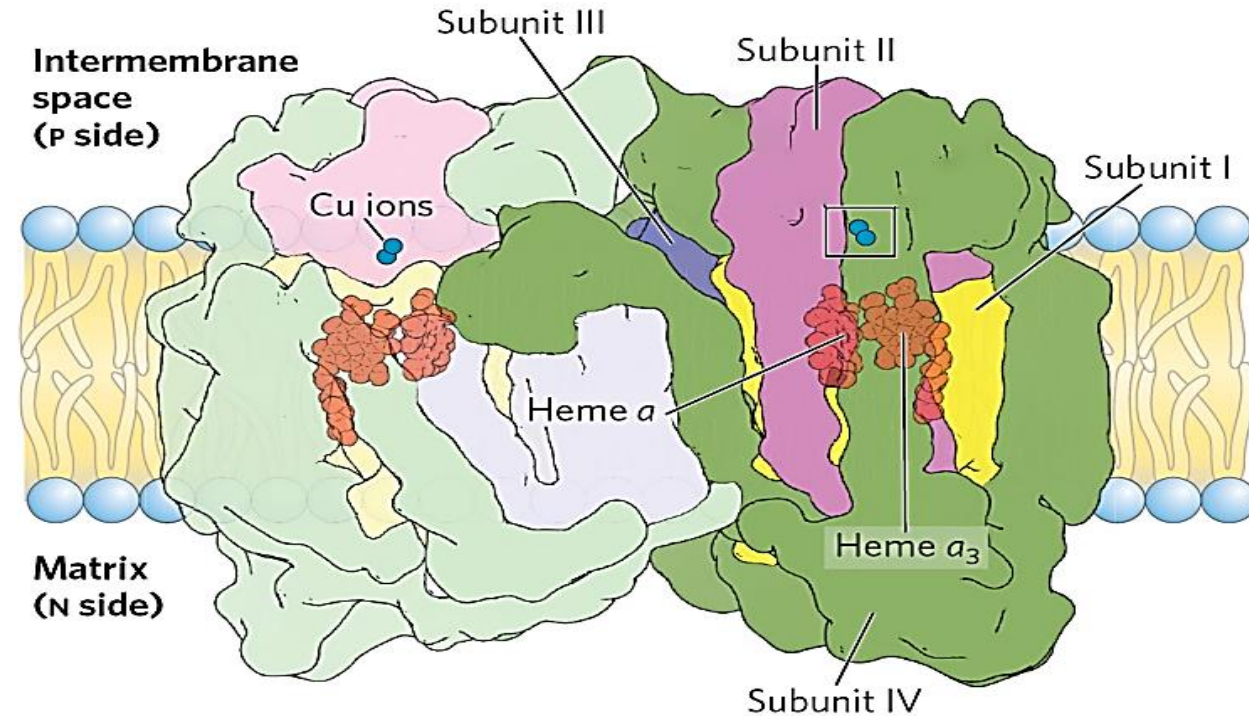
- Meanwhile, on the P side of the membrane, two molecules of QH₂ are oxidized to Q, releasing two protons per Q molecule (four protons in all) into the intermembrane space.



Complex IV of ETC

Complex III الـ *Cytochrome c* الـ *oxidation* الـ *acceptor* من *Complex III*

- Names: Cytochrome oxidase
- Carries electrons from cytochrome c to final e^- acceptor molecular oxygen, reducing it to H_2O .
- Complex IV is a large, dimeric enzyme of the inner mitochondrial membrane, each monomer having 13 subunits



Complex IV of ETC (3 subunits) (1/11/11)

Subunit I has two heme groups (a and a_3) near a single copper ion, Cu_B . Heme a_3 and Cu_B form a binuclear Fe-Cu center.

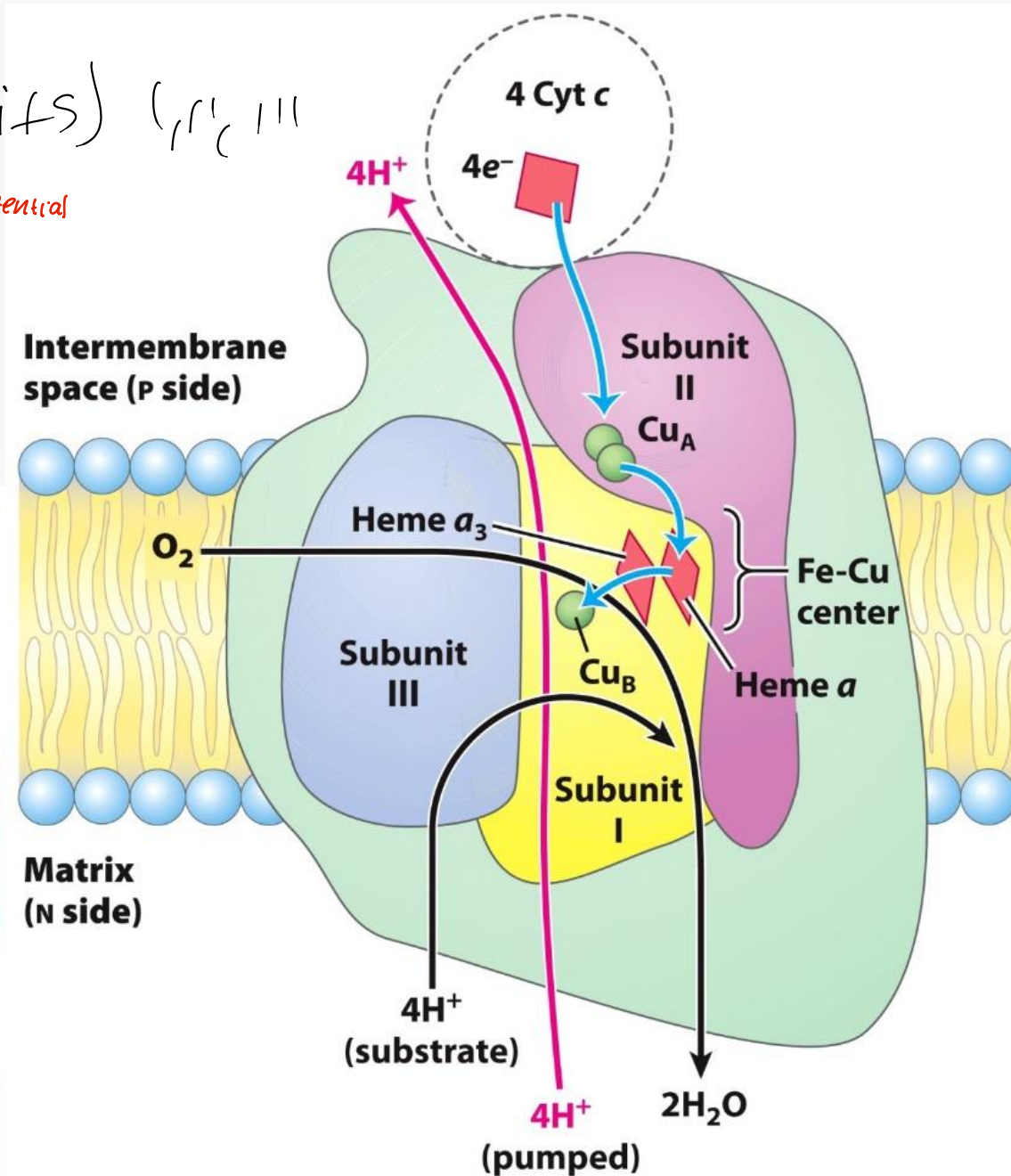
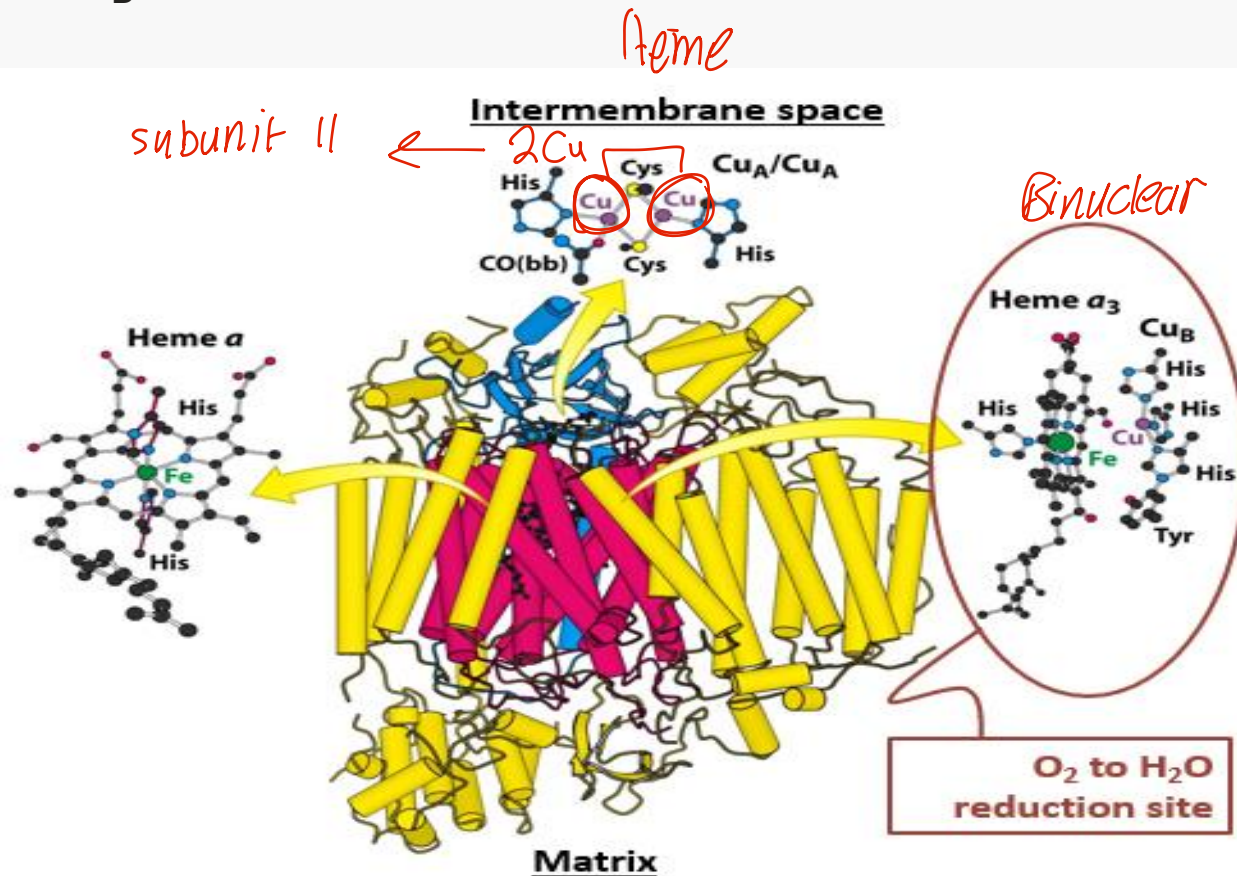


Figure 19-14
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Complex IV of ETC

- Subunit II contains two Cu ions and cytochrome c-binding site.
- Subunit III is essential for rapid proton movement.
- The roles of the other 10 subunits in mammalian Complex IV are not fully understood, although some function in assembly or stabilization of the complex.

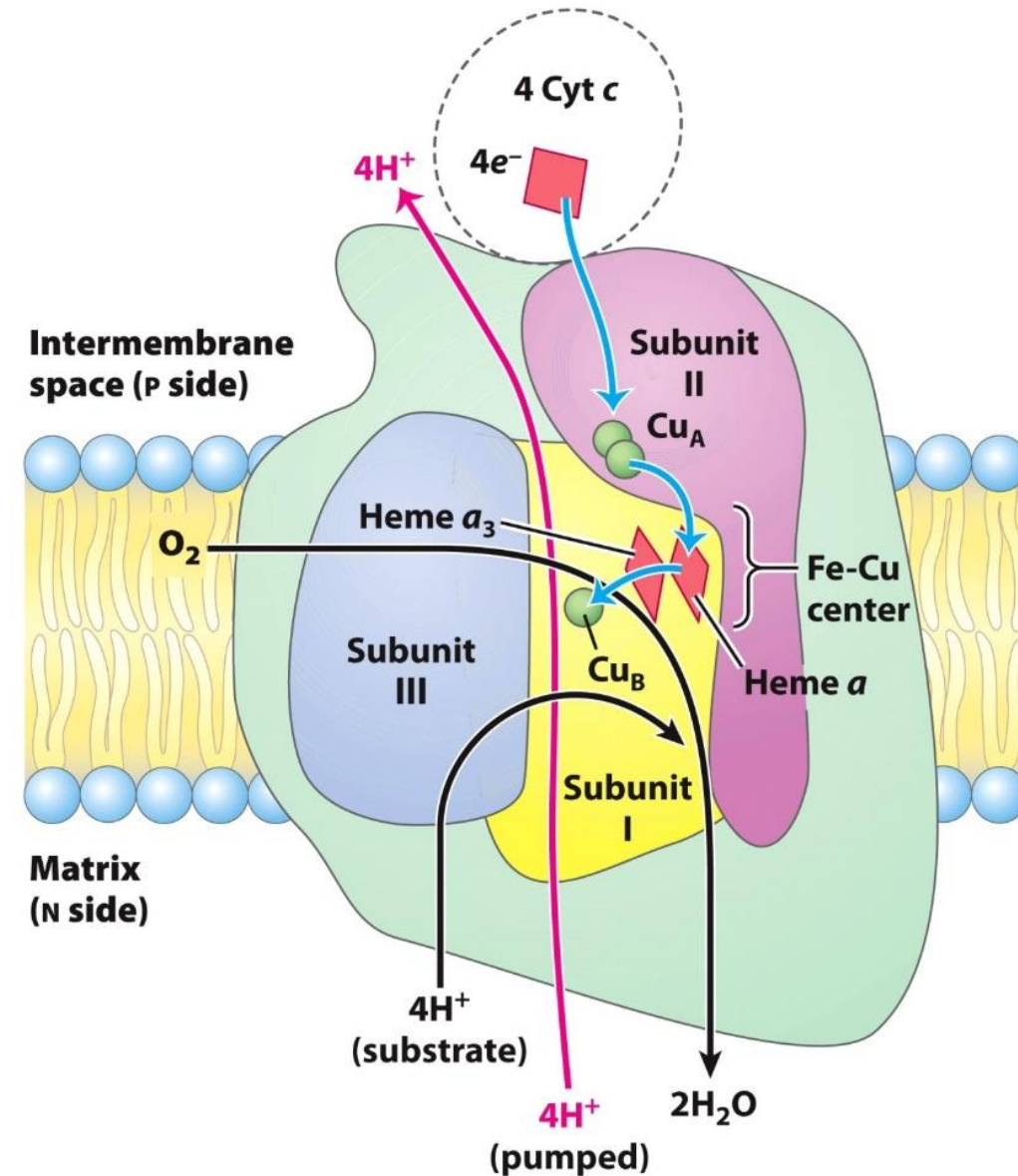


Figure 19-14
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في 2 صه كل واحد نأخذ بعض $1e^-$ لأنه بغيره لا يسير $1e^-$ وبعدها لا تسير
 لا A Cu وبعدها $Cyt c$
 بضع وبعدها الثاني

4 Cyt c
 4e-
 4H+

-
- The diagram illustrates the mitochondrial electron transport chain (ETC) embedded in a lipid bilayer membrane. The membrane separates the **Intermembrane space (P side)** (top) from the **Matrix (N side)** (bottom). The ETC consists of several protein subunits: **Subunit I** (yellow), **Subunit II** (pink), and **Subunit III** (blue). Electrons (e⁻) flow from **Cu_A** to **Cu_B** and then through the **Fe-Cu center** and **Heme a** to **Heme a₃**. This electron flow is coupled with the pumping of protons (H⁺) from the matrix to the intermembrane space. Specifically, **4H⁺ (substrate)** are taken from the matrix, and **4H⁺ (pumped)** are released into the intermembrane space. The final electron acceptor is **O₂**, which is reduced to **2H₂O** in the matrix. The resulting proton gradient across the membrane drives ATP synthesis.

M. ELEYAN

Path of electrons through Complex IV

From here, electrons pass through heme a to the Fe-Cu center (heme a_3 and Cu_B).

1. Two molecules of cytochrome c sequentially transfer electrons to reduce Cu_B and heme a_3

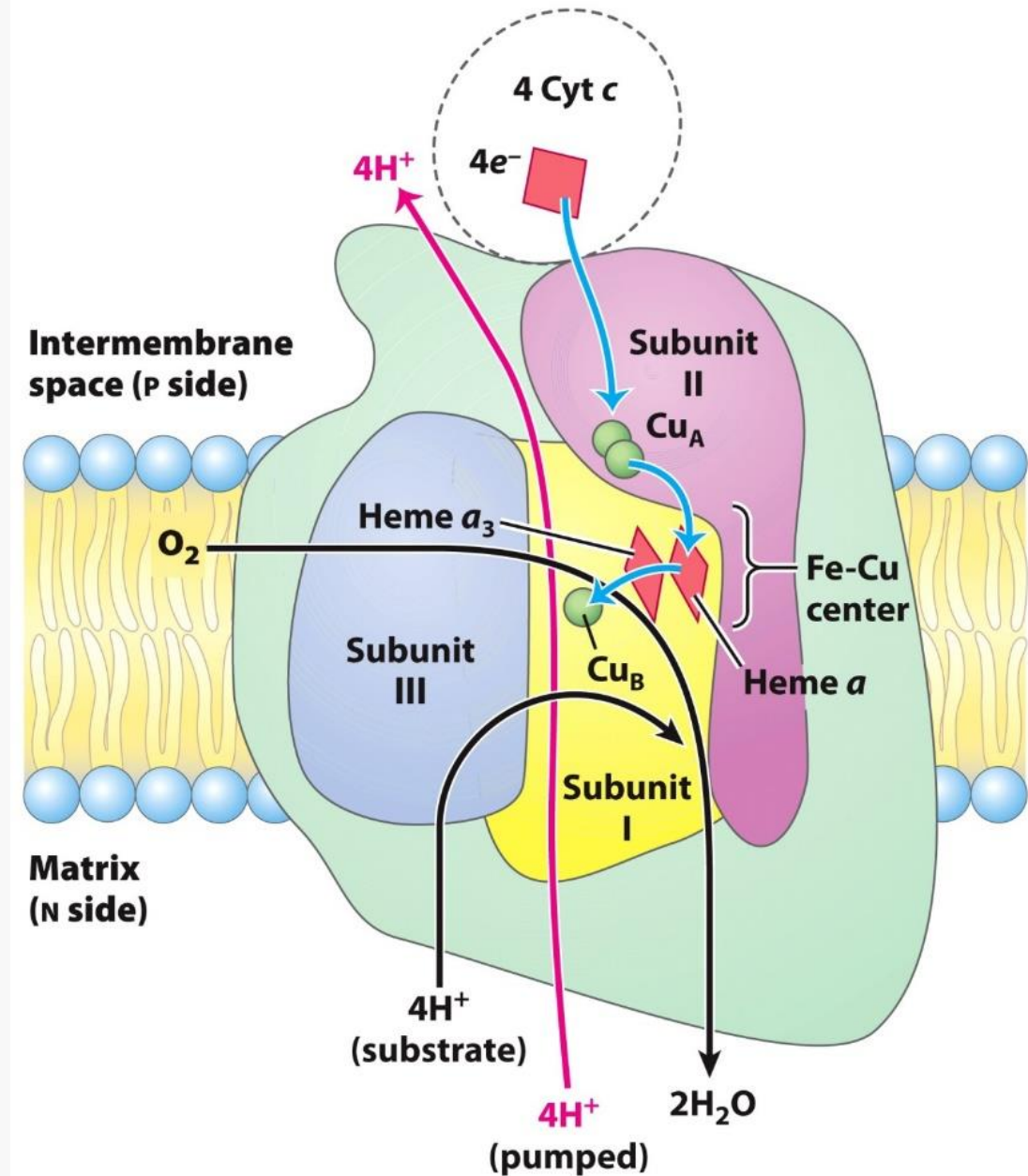
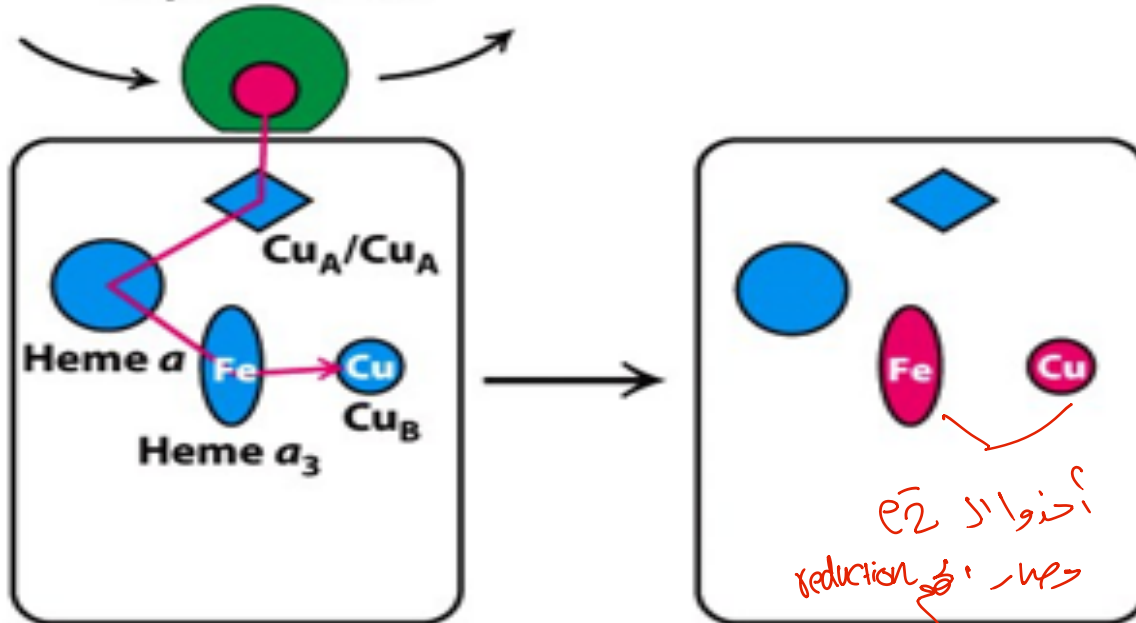
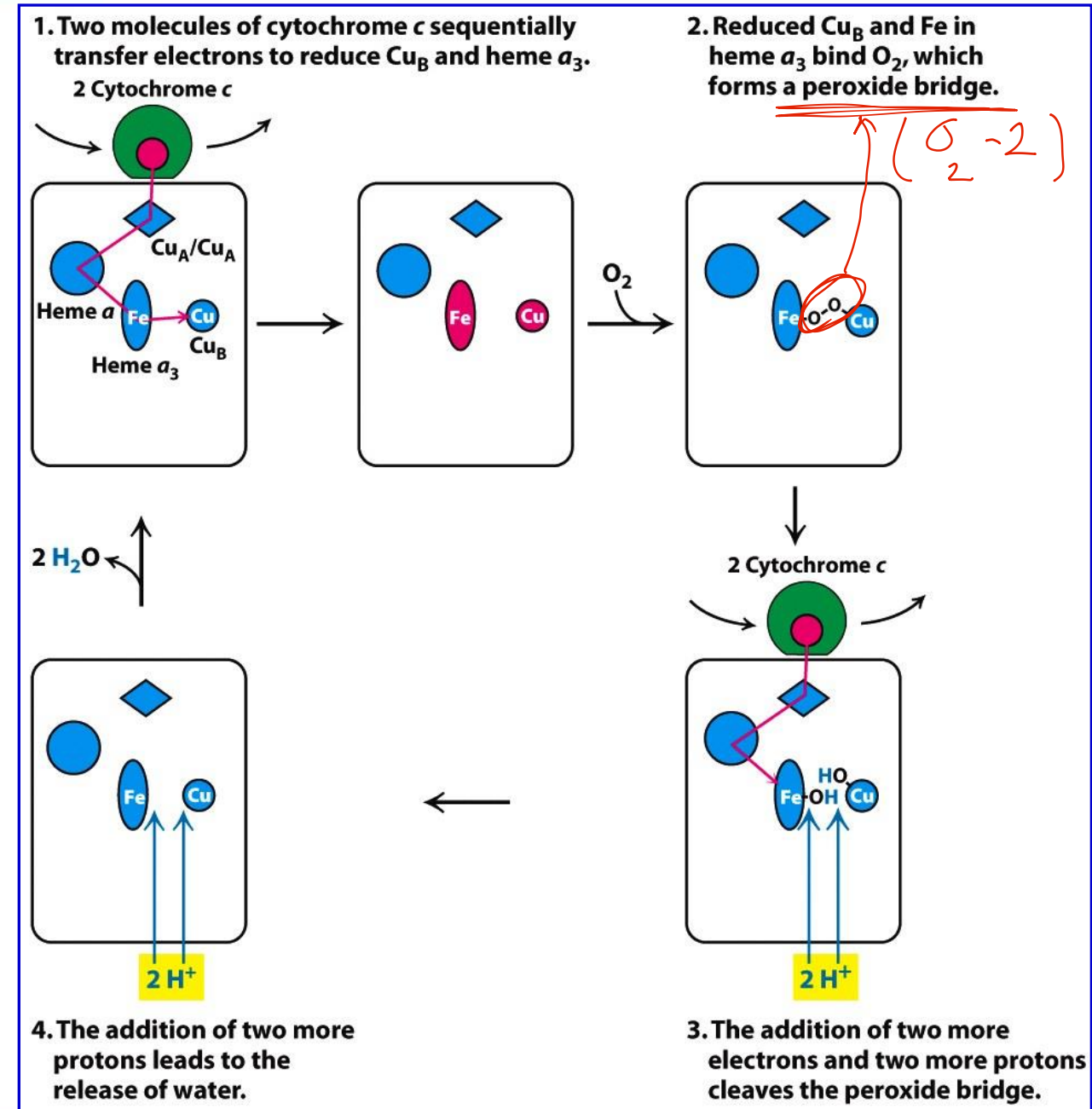


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Path of electrons through Complex IV

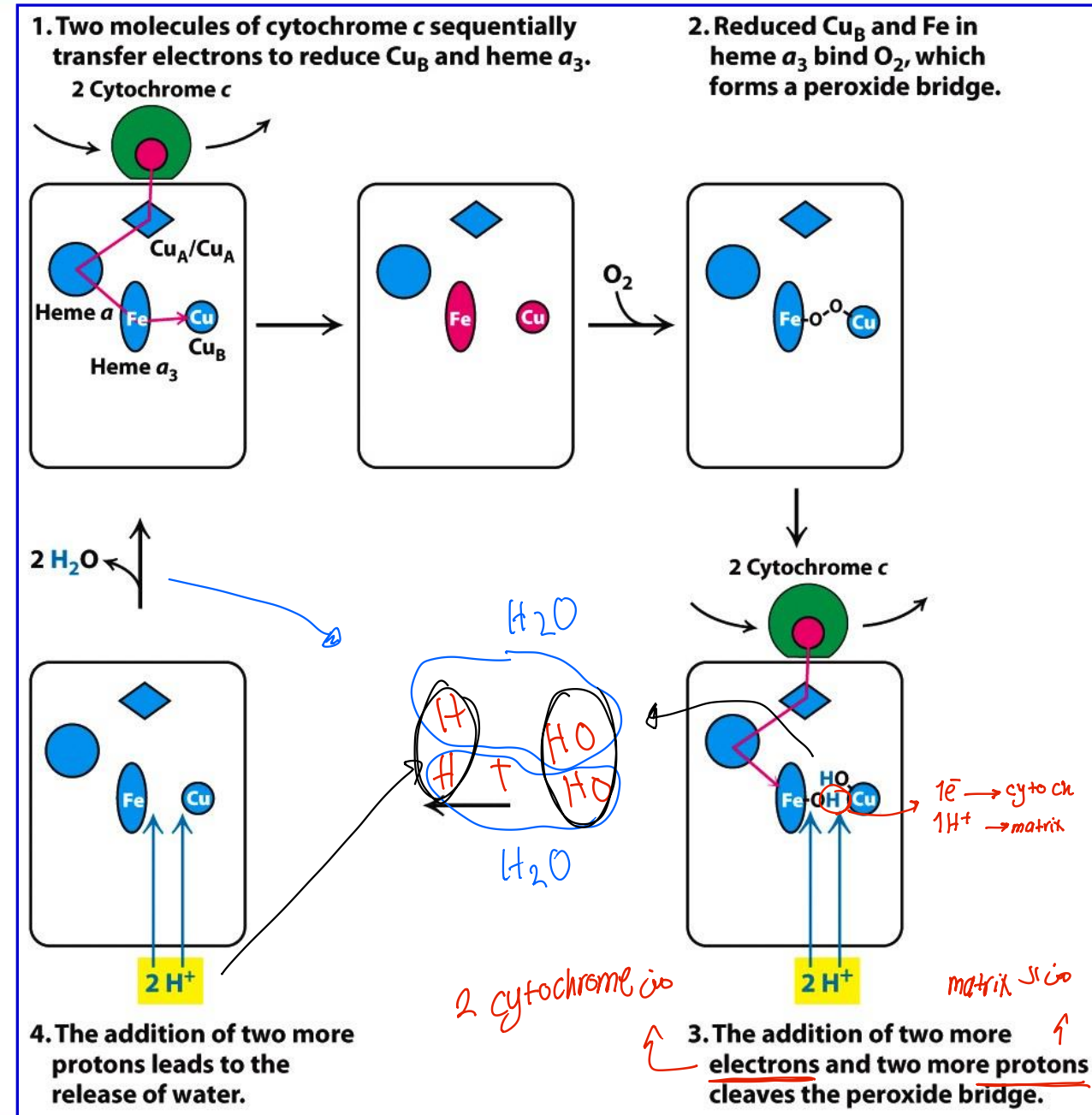
- Oxygen now binds to heme a₃ and is reduced to its peroxy derivative (O_2^{-2}) by two electrons from the Fe-Cu center.



Path of electrons through Complex IV

- Delivery of two more electrons from cytochrome c (top), for a total of four electrons, converts the O_2^{-2} to two molecules of water, with consumption of four “substrate” protons from the matrix.

الاستروجين الذي أخذه من $FADH_2$ و $NADH$ من الميتوكوندريا
 راح يتوجه إلى final acceptor O_2 في الميتوكوندريا



- At the same time, four protons are pumped from the matrix for every four electrons passing through Complex IV.

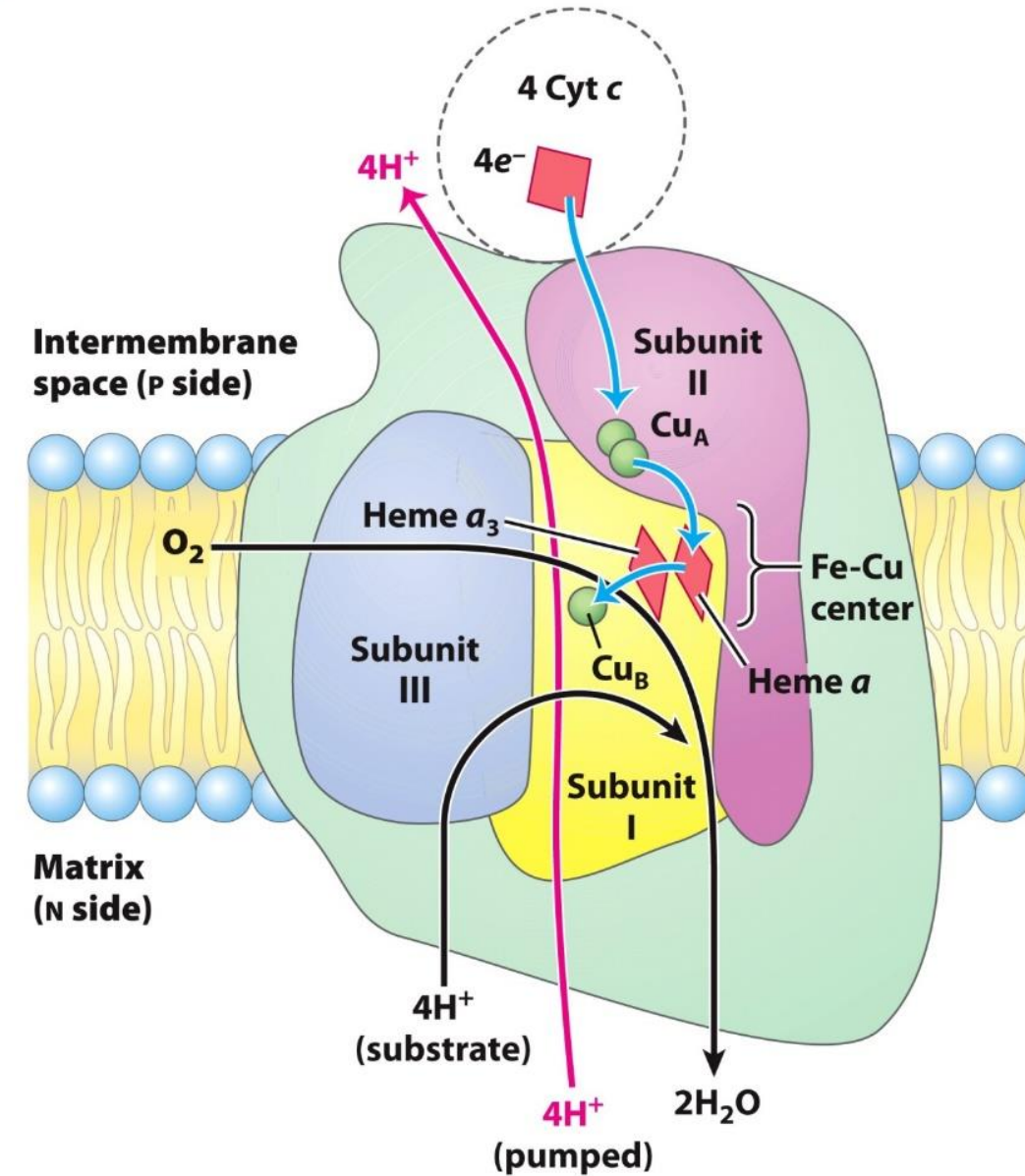
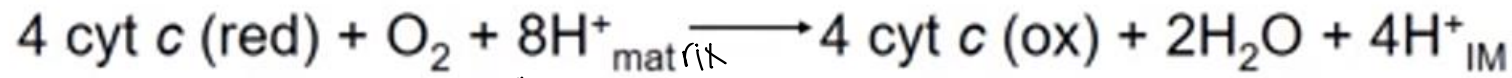
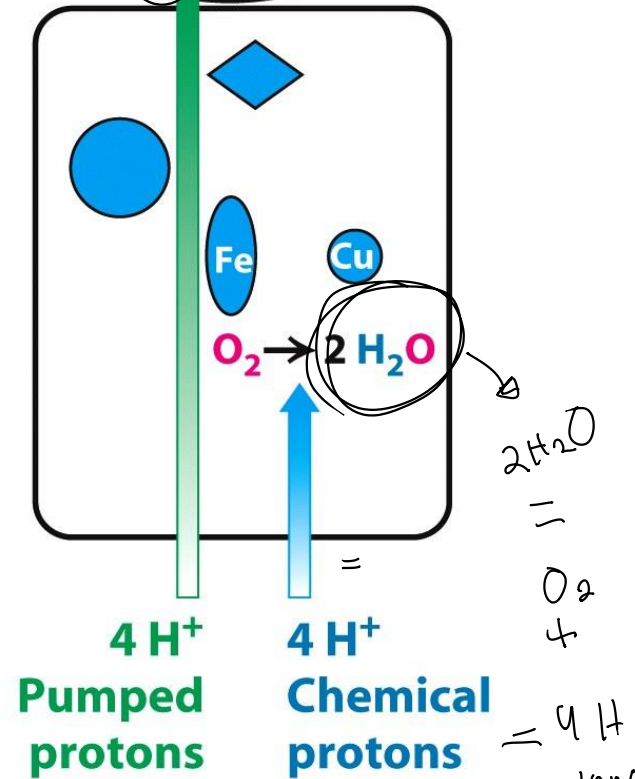
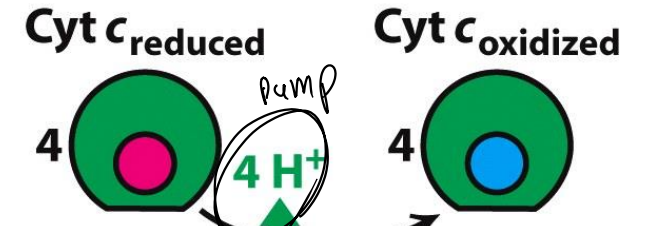
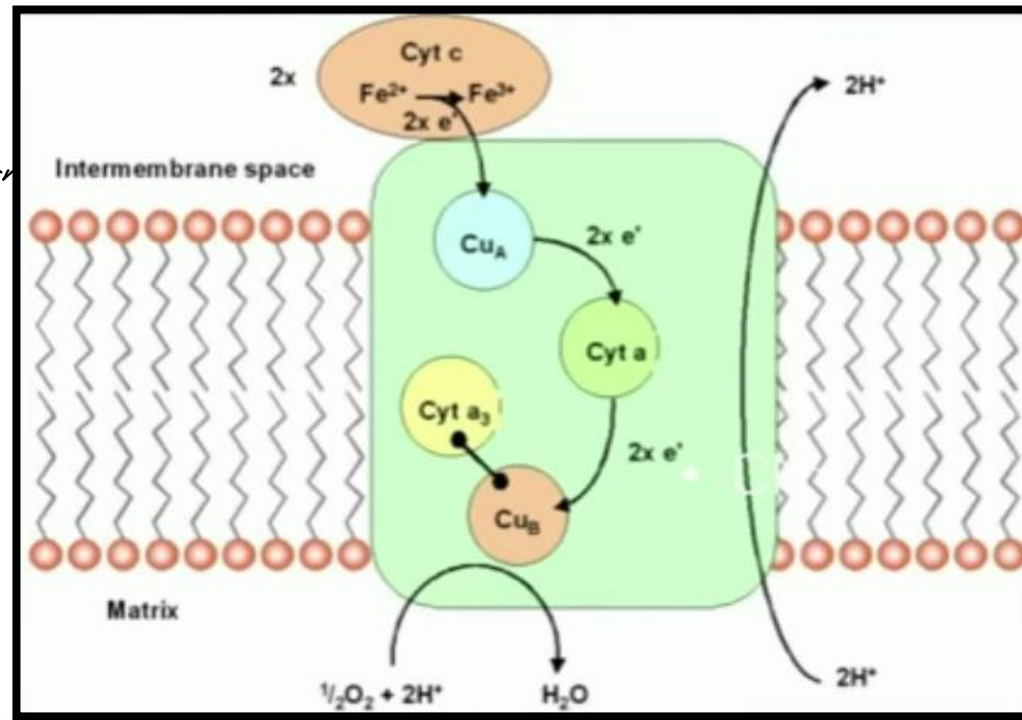


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A simplified reaction sequence is presented here



Handwritten notes for the reaction equation:
 4H^+ (from matrix) → 4 pumped
 O_2 (molecular) → 2 H_2O



Handwritten note: + 4e⁻ cyto c in

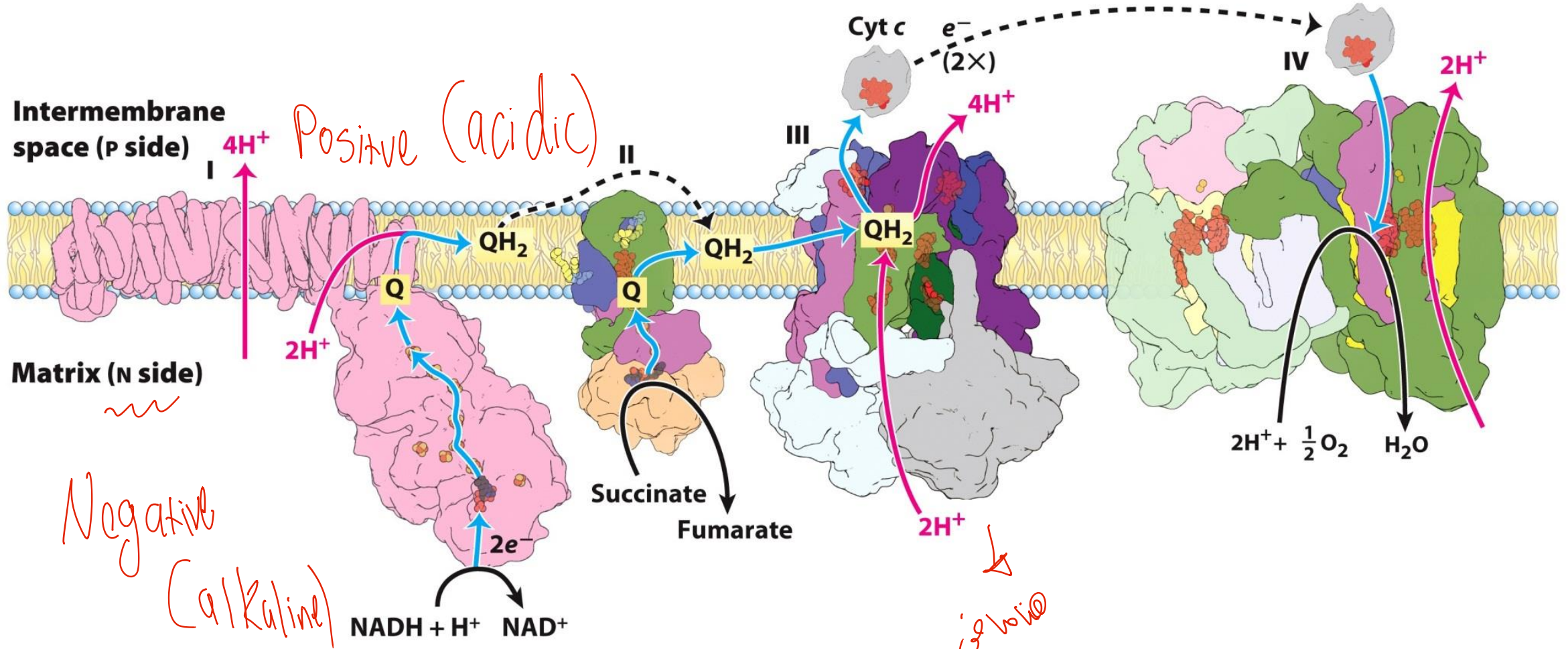


Figure 19-16

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Pumping protons

Mitochondrial Electron-Transport Chain Components

Table 19.2 Components of the mitochondrial electron-transport chain

Enzyme complex	Mass (kd)	Subunits	Prosthetic group	Oxidant or reductant		
				Matrix side	Membrane core	Cytoplasmic side
NADH-Q oxidoreductase	>900	46	FMN Fe-S	NADH	Q	
Succinate-Q reductase	140	4	FAD Fe-S	Succinate	Q	
Q-cytochrome c oxidoreductase	250	11	Heme b_H Heme b_L Heme c_1 Fe-S		Q	Cytochrome c
Cytochrome c oxidase	160	13	Heme a Heme a_3 Cu_A and Cu_B			Cytochrome c

BioVisions

at Harvard University

biovisions.mcb.harvard.edu

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Chemiosmotic Model

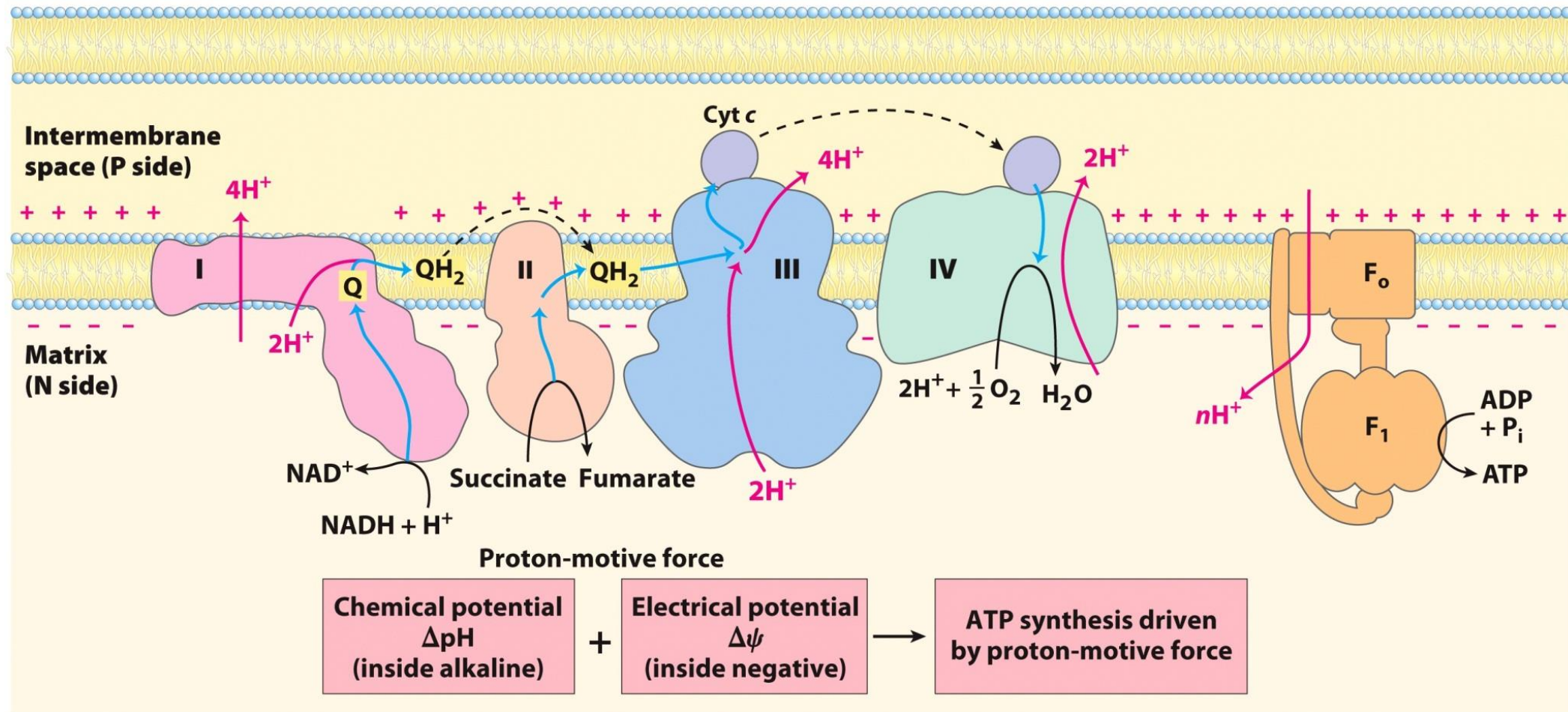
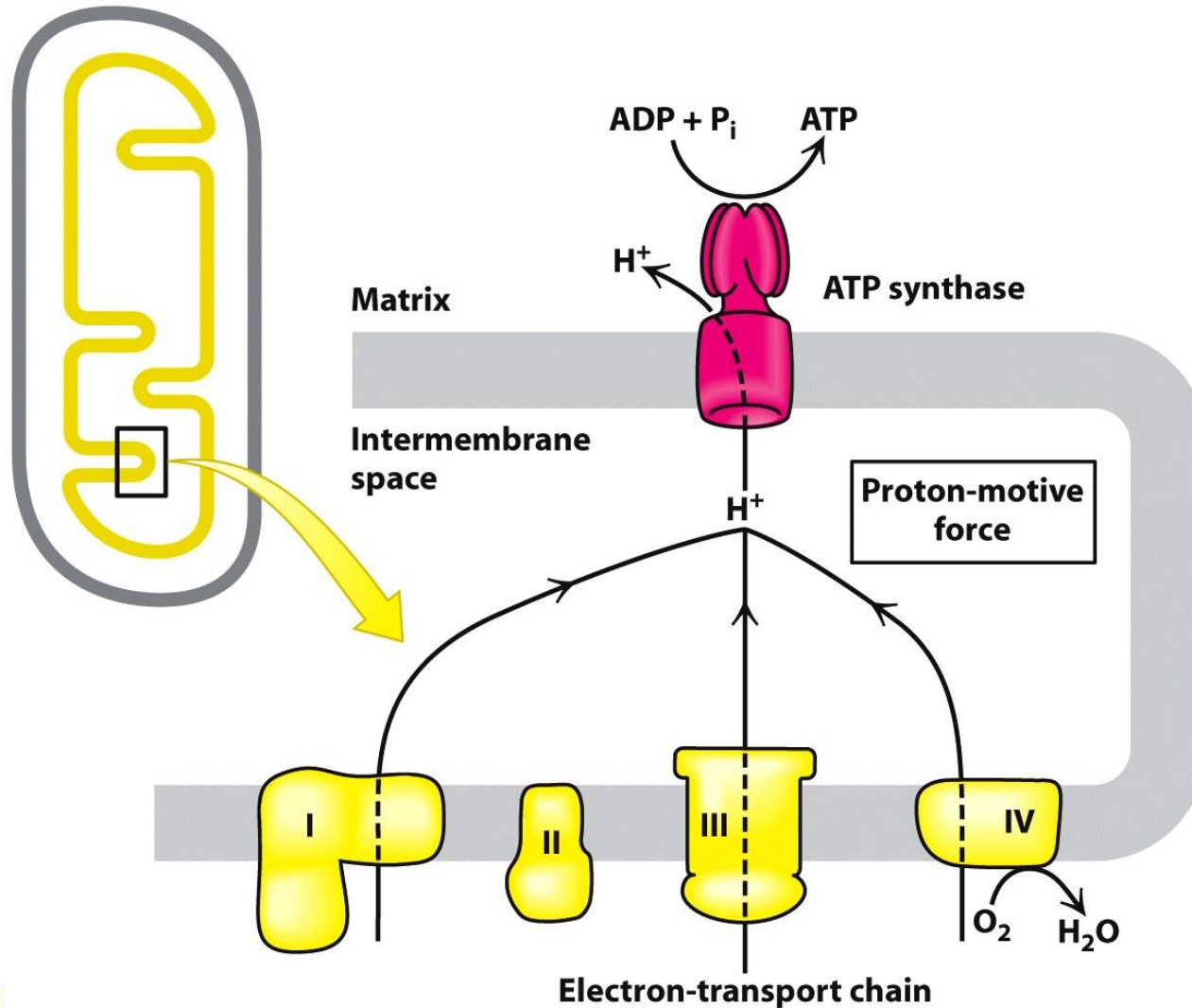


Figure 19-19

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ATP Synthesis via a Proton Gradient



The two major 20th century biological discoveries:

DNA structure and
ATP synthesis

Mitochondrial ATP synthase complex

Complex V, also known as **ATP synthase**, is a complex molecular machine that catalyzes the synthesis of ATP from ADP and inorganic phosphate (P_i) using the energy stored in a proton gradient across the inner mitochondrial membrane.

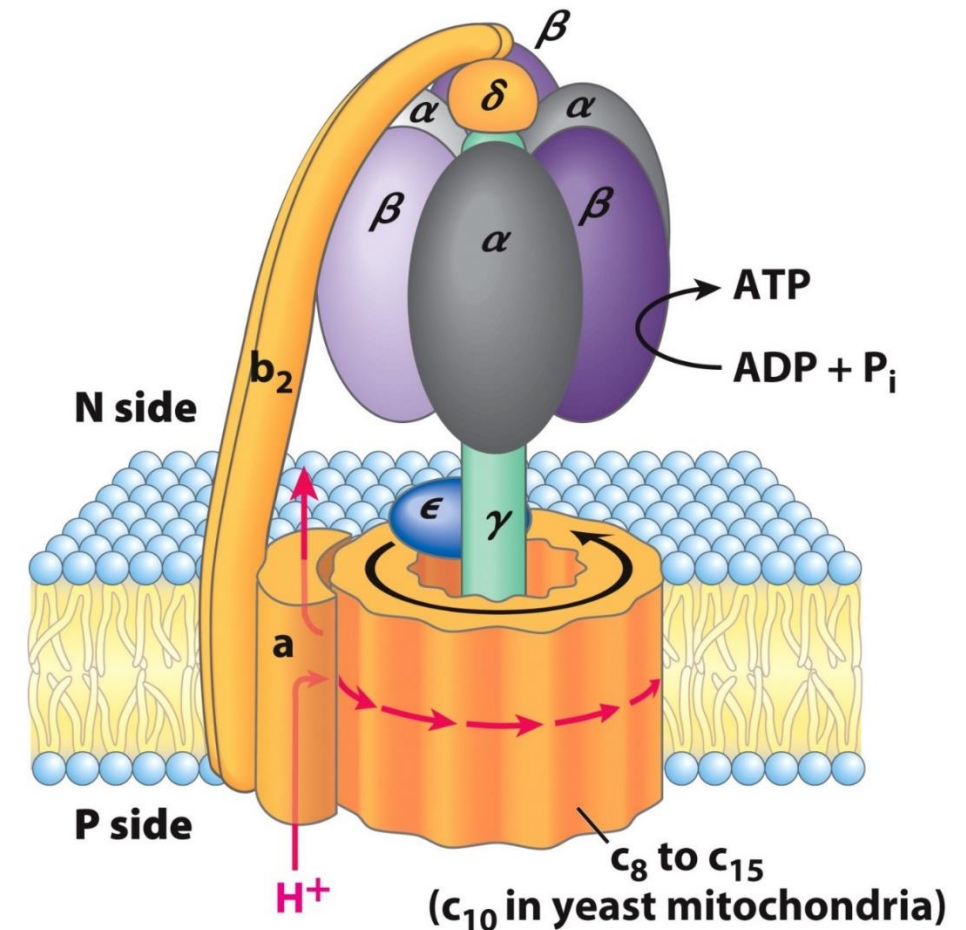
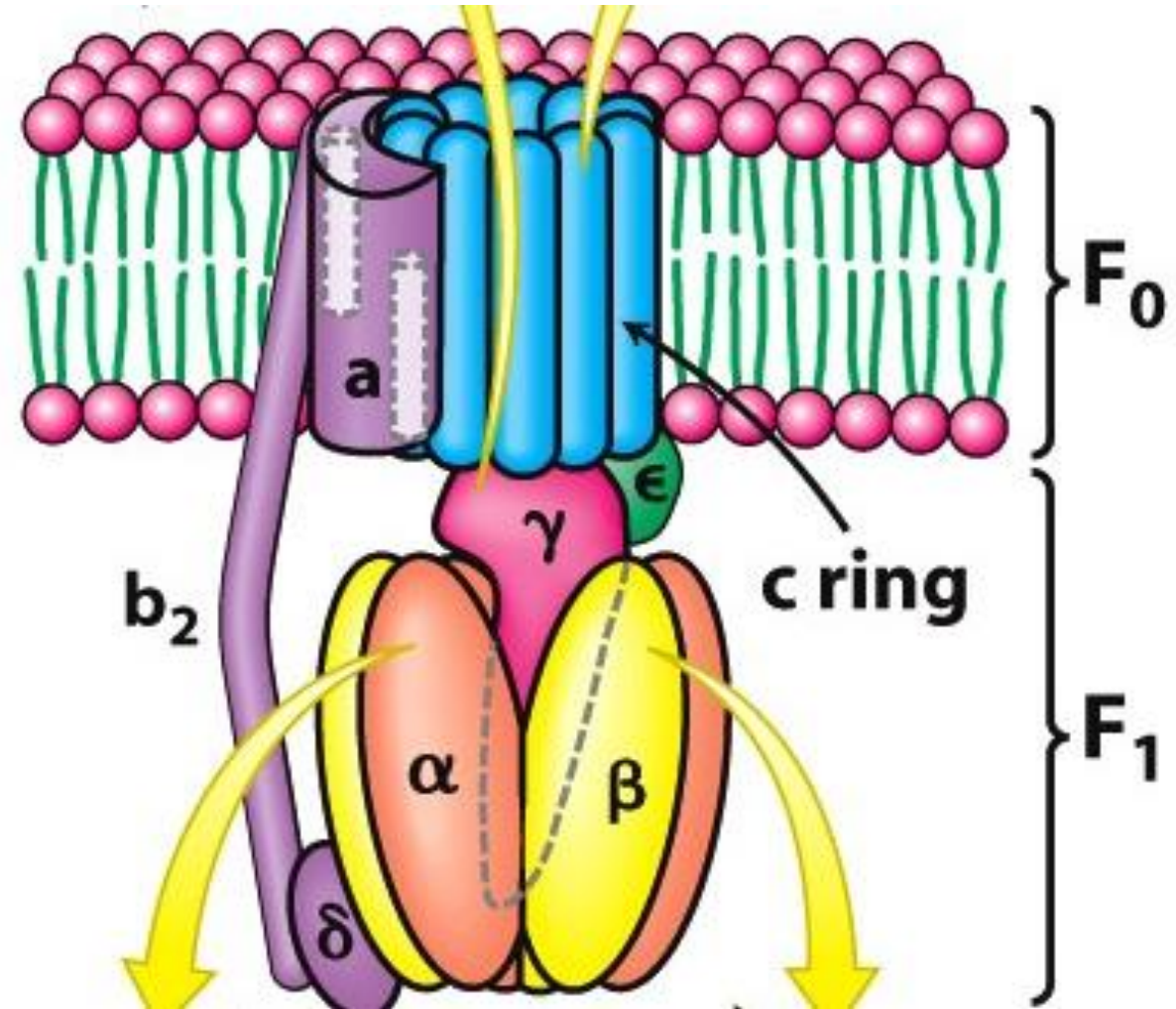


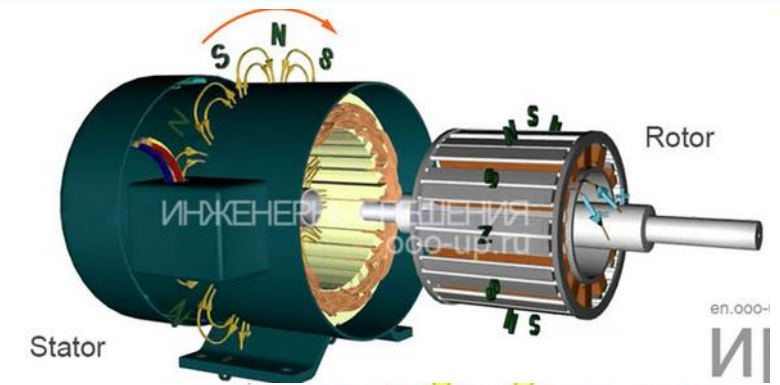
Figure 19-25a
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Structure of ATP Synthase

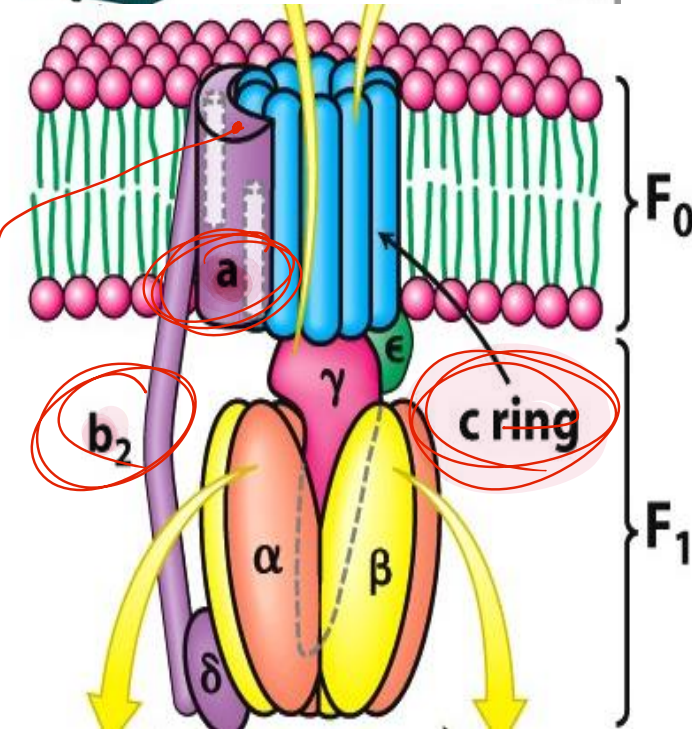
- ATP synthase is composed of two main components:
 1. Proton-Conducting (F_0) complex
 2. Catalytic (F_1) complex



ATP Synthase



- **F₀ complex:** Embedded in the inner mitochondrial membrane and consists of a, b, and c subunits
- C subunit (ring) is embedded in the membrane, comprising 8-15 subunits, rotor ring.
 شاكها دائري وابع طوله دوران عرضها 8-15
 الجزء القوي F₁
 متصلة مع خارج الحلقة
- A subunit binds to the outside of the ring, , it forms a proton channel
- B subunit is an extended arm to f₁ complex to stabilize it.

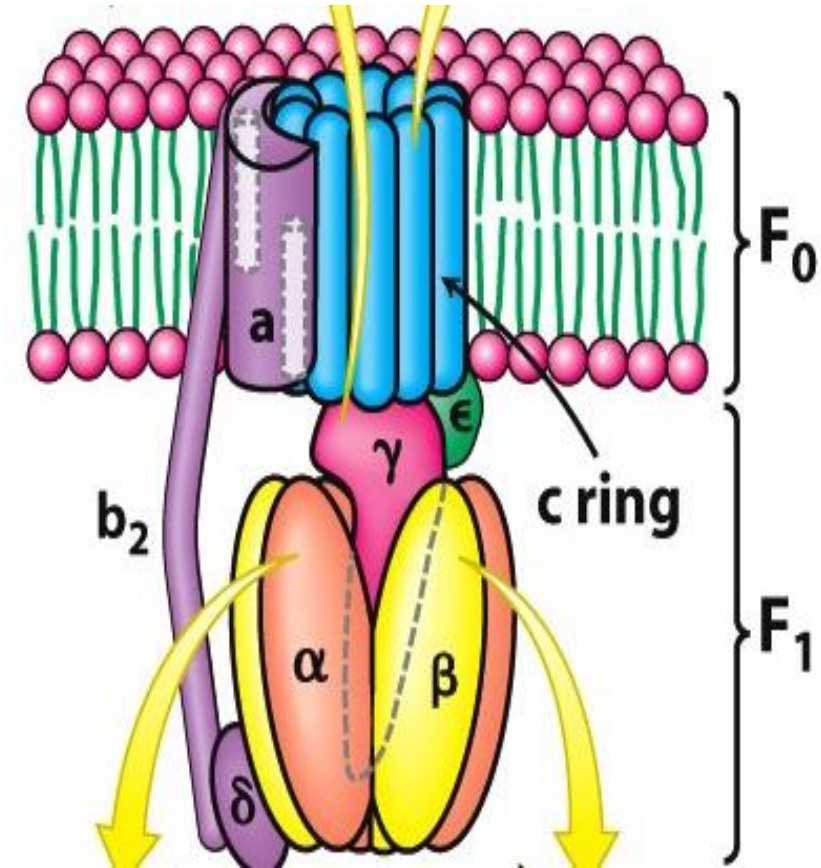


ATP Synthase

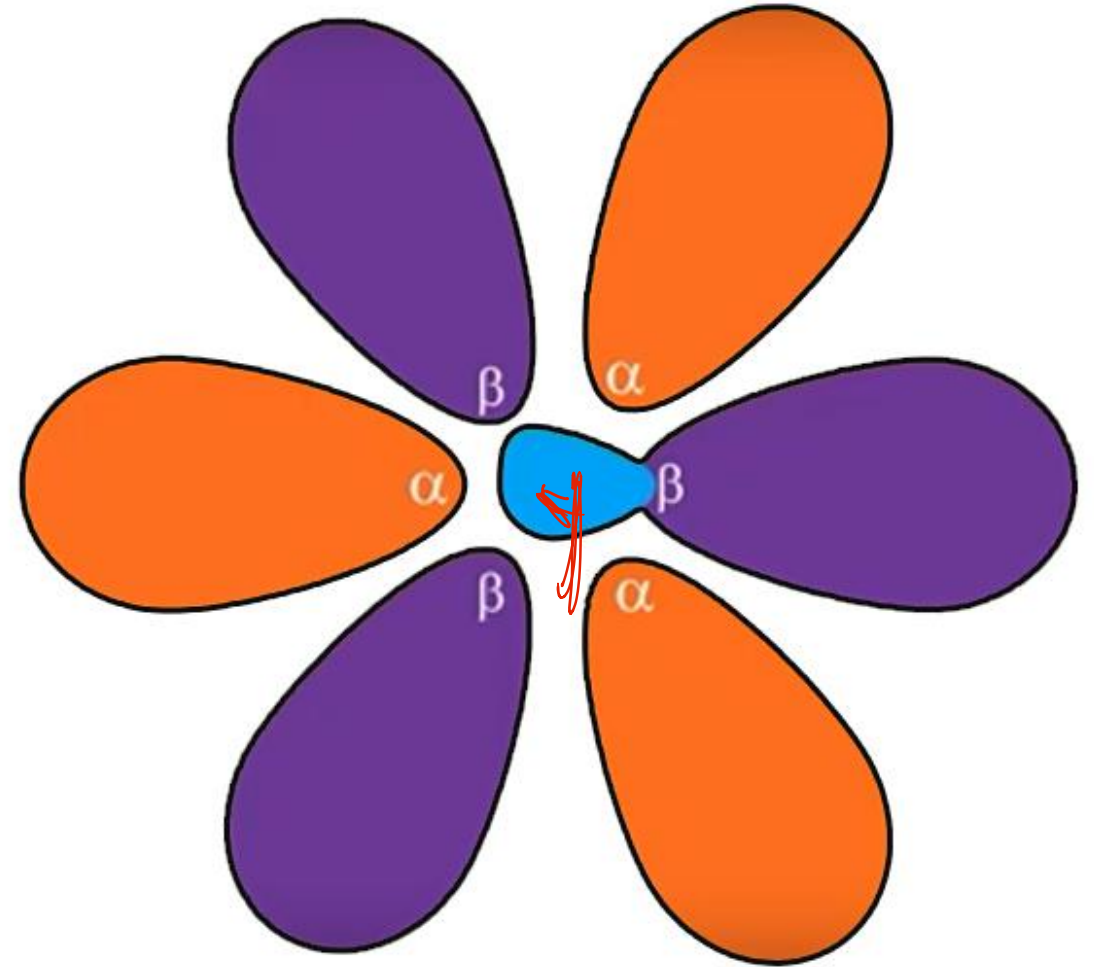
F₁ contains: *مركبة -6*
التي ترتبط مع O₂ في F₀
 α_3, β_3 hexameric ring, central stalk (γ, ϵ), and δ

Some texts: central stalk and C-ring form the rotor and remaining molecule is the stator

مع جوف
هم الـ motor
الذي يتحركوا



- The F1 subunit of ATP synthase has 3 α and 3 β subunits.
- Alternating α and β subunits are arranged in a hexamer.
- The γ subunit is a central shaft.
- Each of the β subunits has a catalytic site for ATP synthesis.



β -empty, β -ADP, or β -ATP.

Each β subunit alternates between conformations,

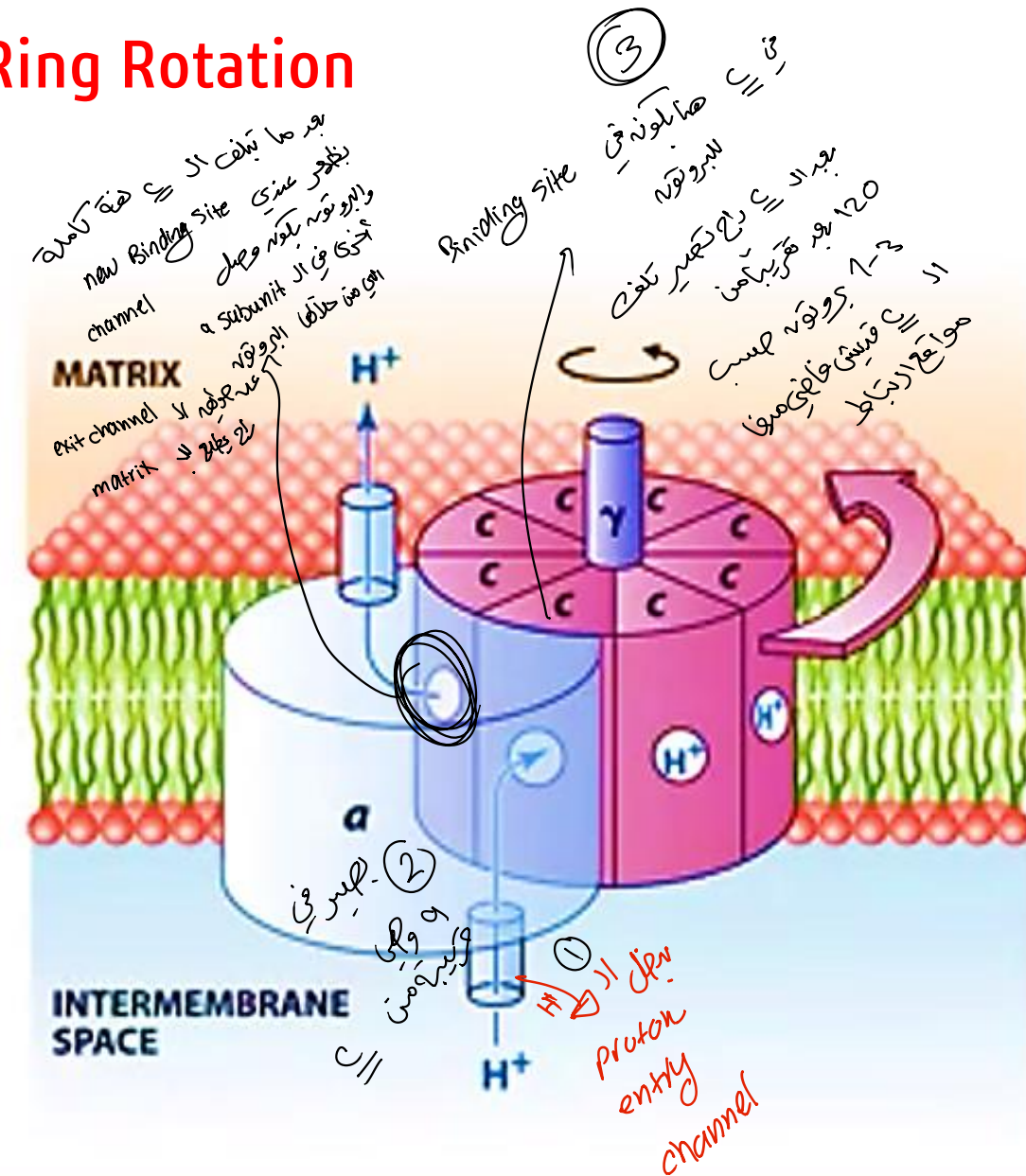


Proton Motion Across the Membrane Drives C-Ring Rotation

H^+ enter the a subunit through proton entry channel, this allows the H^+ to access to c-subunit

The c-ring rotates 120 degree and expose new H^+ binding site

Proton exit channel: This channel allows protons to exit the a subunit into the mitochondrial matrix.

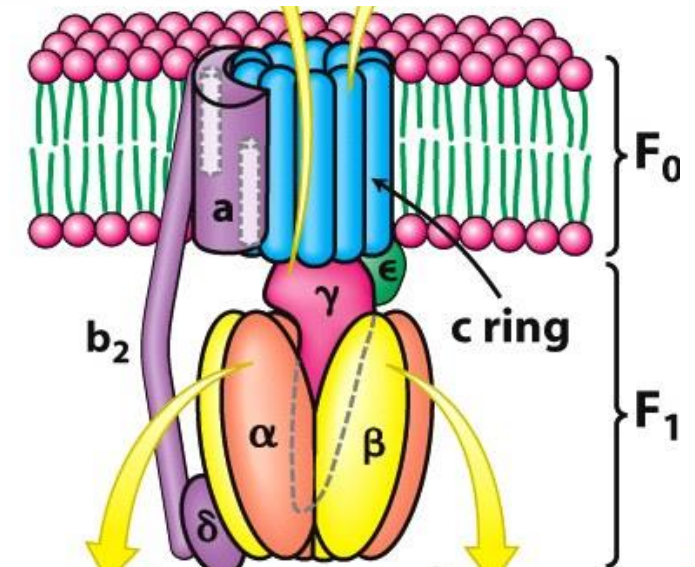
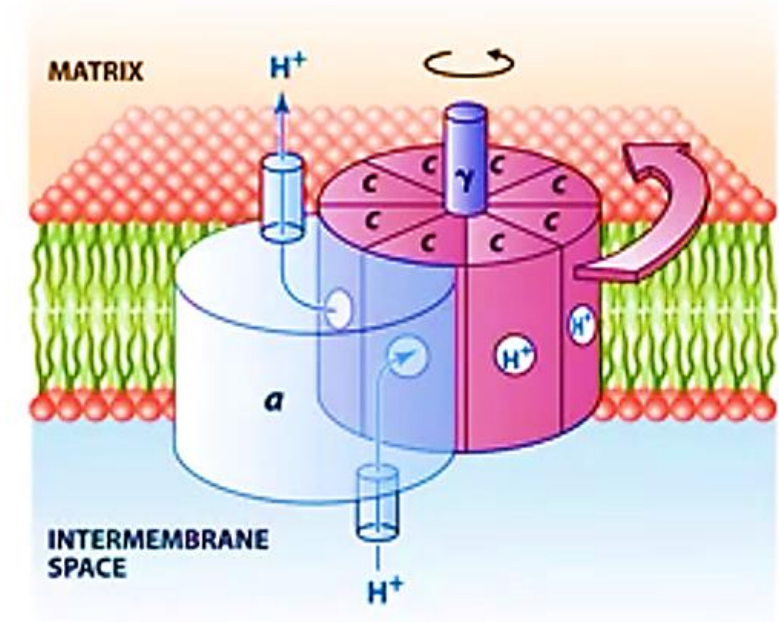


C-Ring Tightly Linked to γ and ϵ Subunits

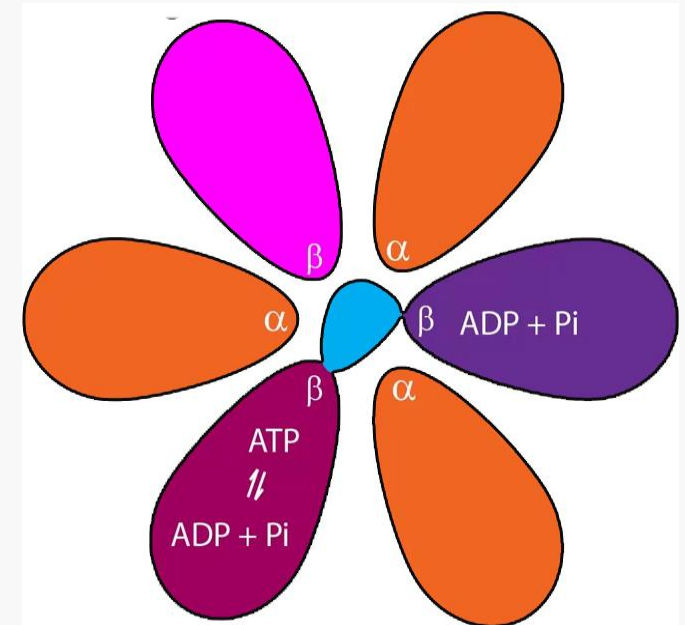
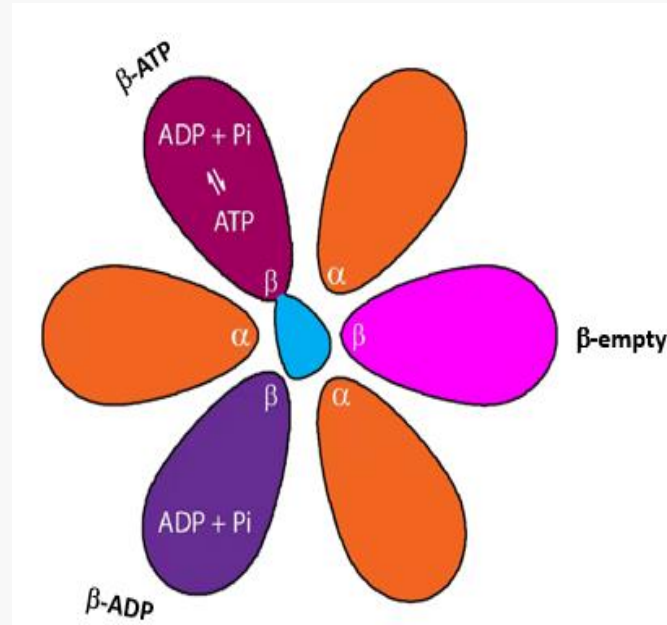
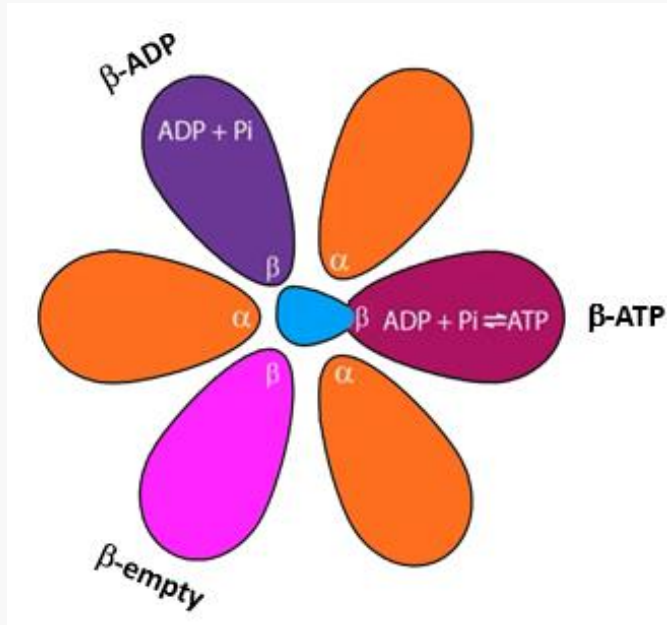
The rotation of the c-ring drives the rotation of the central stalk (γ and ϵ) inside the $\alpha_3\beta_3$ hexamer unit of F_1

The b with δ subunits (prevent rotation of the α_3 and β_3 hexamer unit)

fixation



γ -Rotation Induces a Conformational Shift in the β Subunits



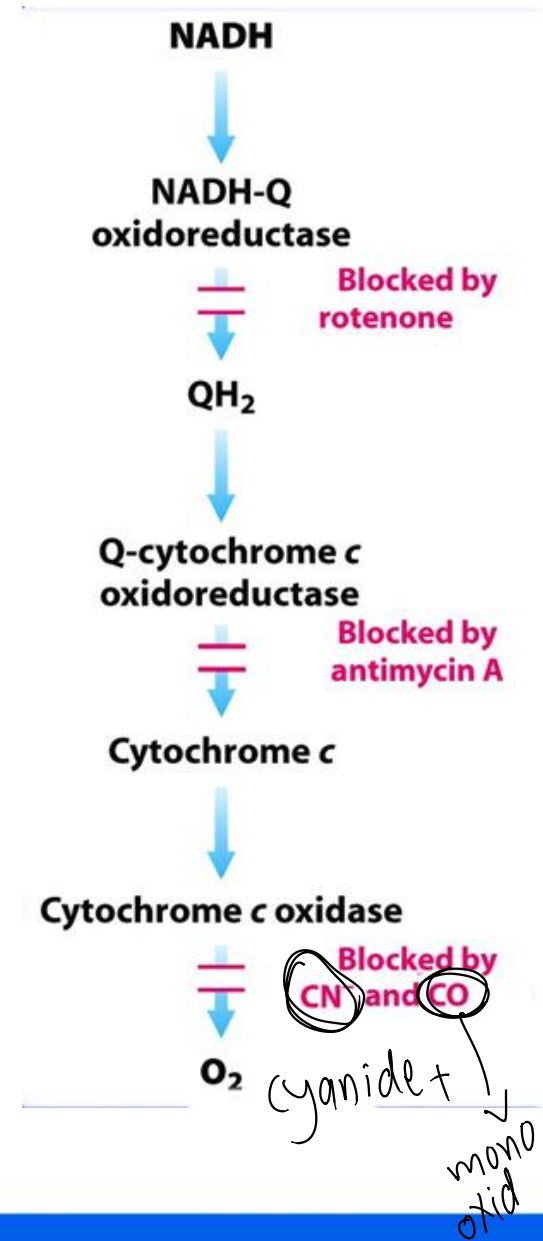
1. When protons pass through F_o the c subunits rotate and rotate the attached γ subunit along with them.
2. With each 120° rotation of the γ subunit, they comes in contact with another β subunit, forcing it to release ATP and enter the β -empty conformation.
3. The empty subunit then binds ADP and P_i and catalyzes the synthesis of another ATP molecule.

ATP Synthase Mechanism

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Electron Transport Chain Inhibitors

- **Rotenone** is a naturally occurring compound found in several plants. It has been used for centuries as a natural insecticide and piscicide.
inhibit complex I
- **Antimycin A** is a natural antibiotic produced by Streptomyces bacteria. It is a potent inhibitor of **Complex III** in the electron transport chain.
+ toxin

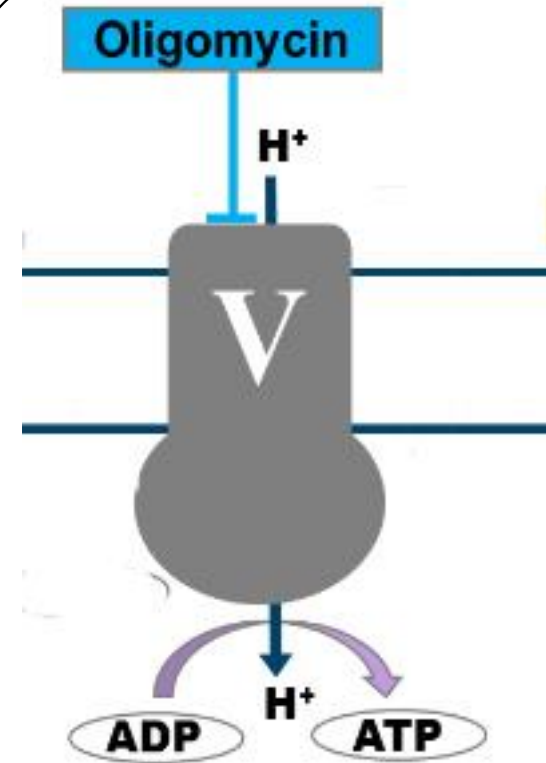


Oligomycin

Complex V

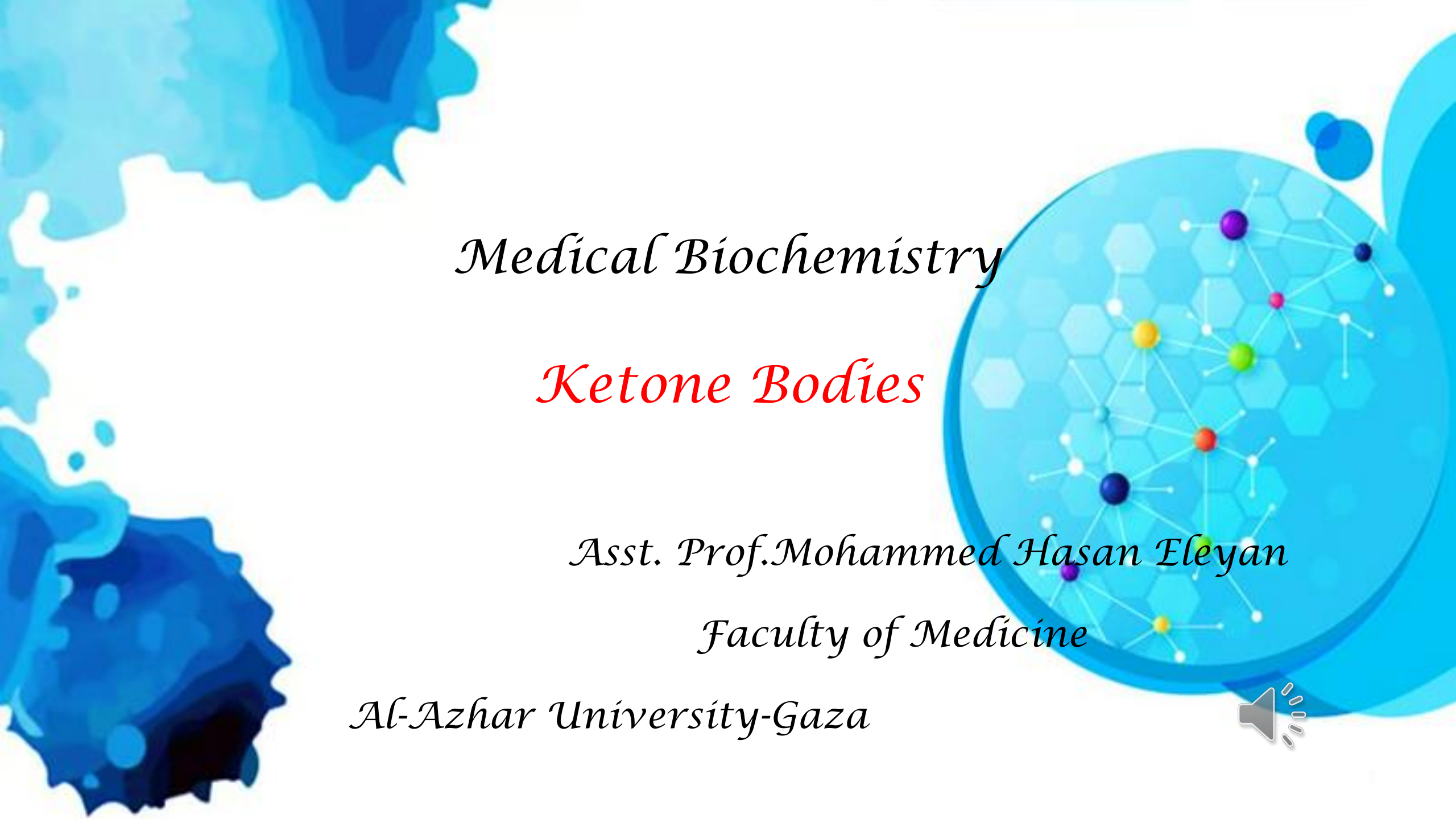
*X inhibition
of eeg
transfer of electrons*

- Oligomycins are antibiotic created by Streptomyces that are strong antibacterial agents but are often poisonous to other organisms, including humans.
- This drug binds to the Fo of ATP synthase, closing the H⁺ channel and preventing reentry of H⁺ into the matrix, thereby inhibiting phosphorylation of ADP to ATP.
- Because the pH and electrical gradients cannot be consumed in the presence of this phosphorylation inhibitor, electron transport stops because of the difficulty of pumping any more H⁺ against the steep concentration gradient. This dependency of cellular respiration on the ability to phosphorylate ADP to ATP is known as respiratory control and is the consequence of the tight coupling of these processes.



Thank you

I know it's too long lecture but this is what is called medicine



Medical Biochemistry

Ketone Bodies

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

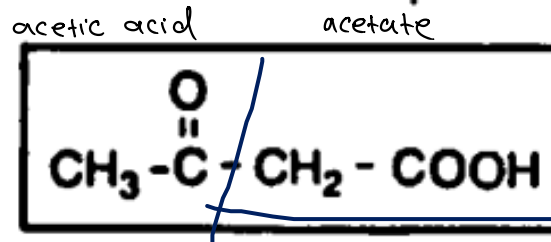
Al-Azhar University-Gaza



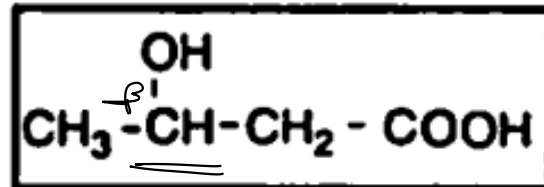
Ketone Bodies

DEFINITION: These are 3 compounds formed by the liver and include:

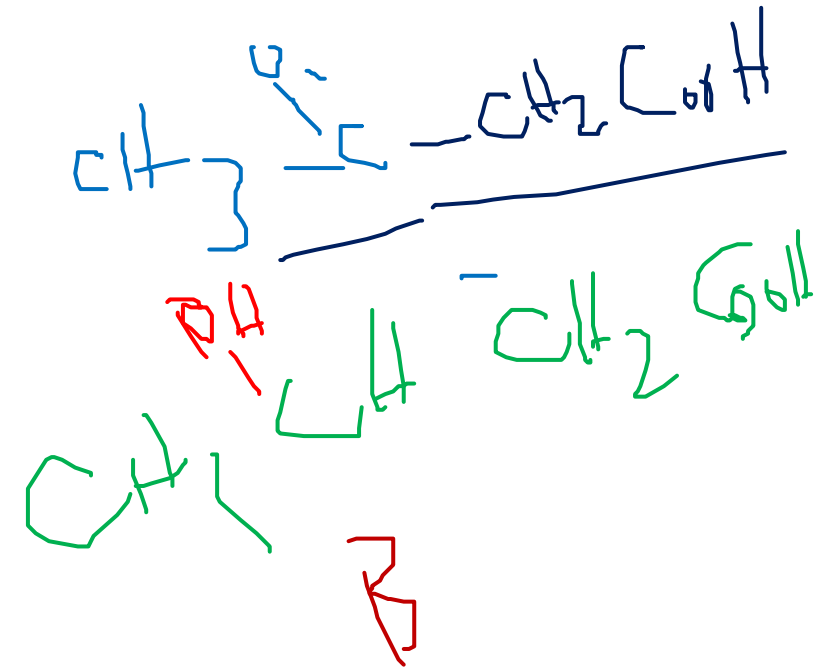
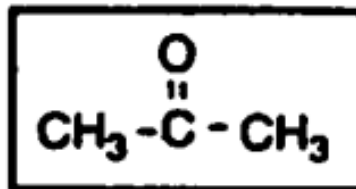
Acetoacetate



β-Hydroxybutyrate



Acetone



Ketone bodies are used as a source of energy

جبر صحتہ تنظیم آکر پس

- They are converted into acetyl-CoA which is oxidized in tricarboxylic acid (TCA) cycle.
- Skeletal muscles, cardiac muscles, kidneys and most of tissues can use ketone bodies as a source of energy in prolonged fasting and starvation.
- Brain tissue can also oxidize ketone bodies within 5 to 6 days of starvation.
- Liver does not contain enzymes for ketone bodies oxidation (ketolysis). Thus liver cannot oxidize them.



Synthesis of ketone bodies (ketogenesis):

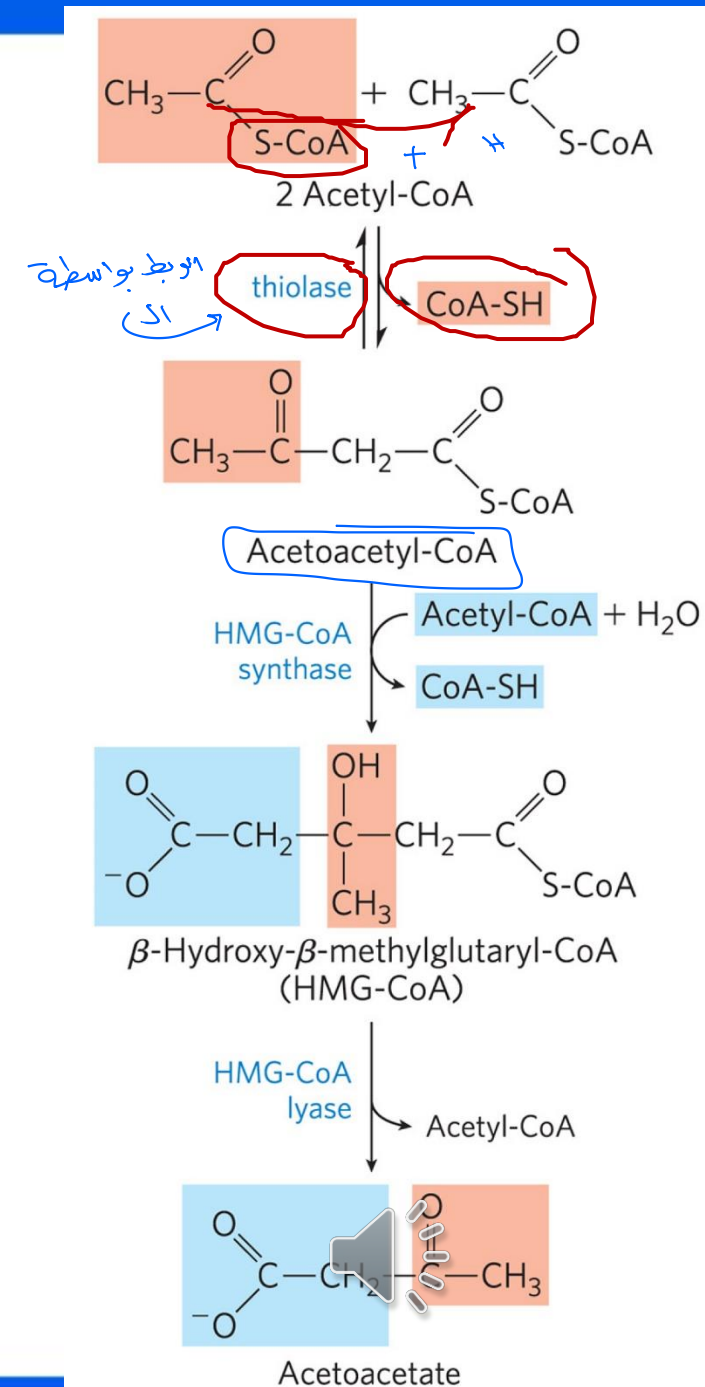
- Site:
 - Organ location: Liver
 - Intracellular location: Mitochondria.
- Precursor: Acetyl CoA

↓
المادة التي ستُحوَّل
لتُصنع الكيتونات



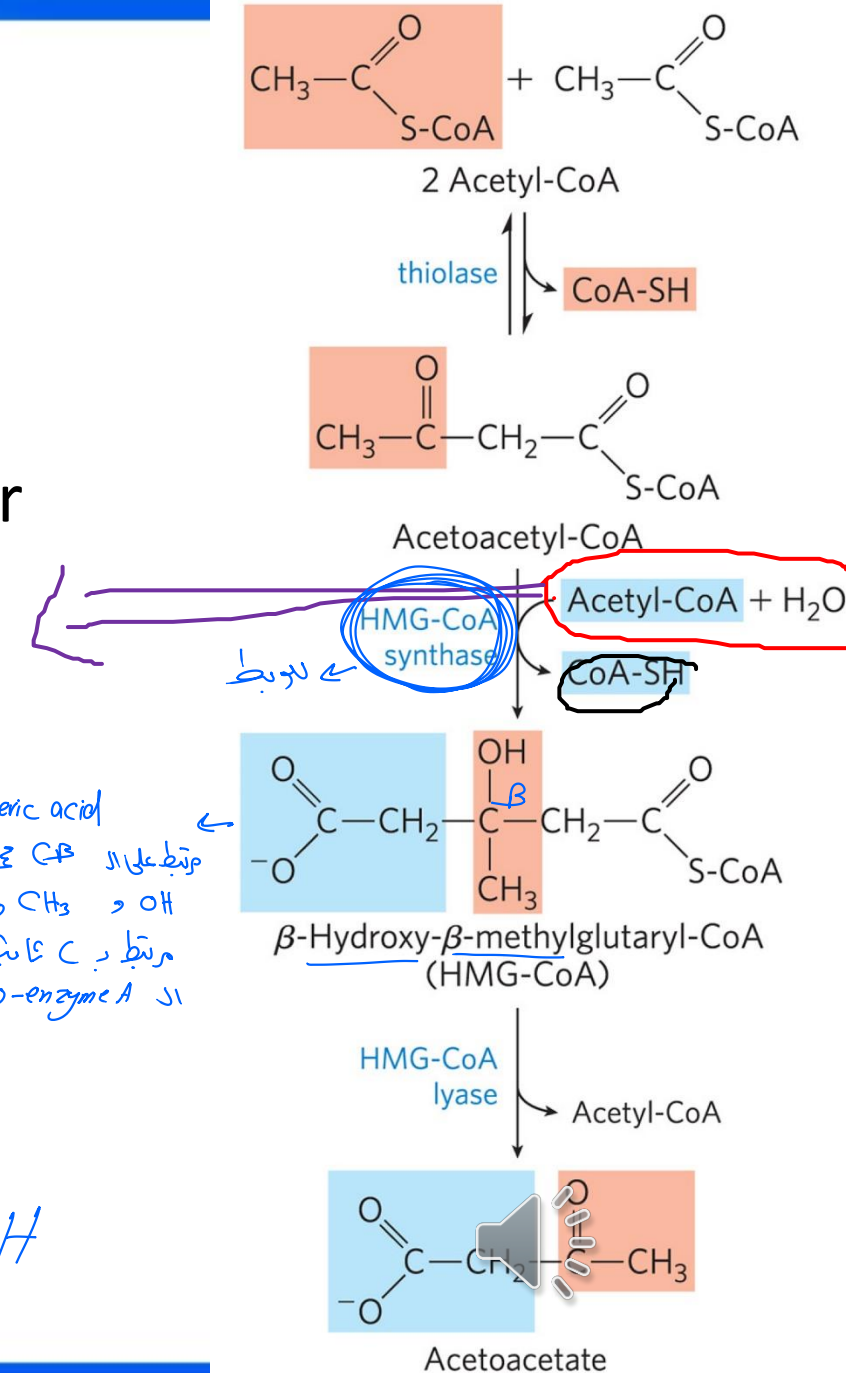
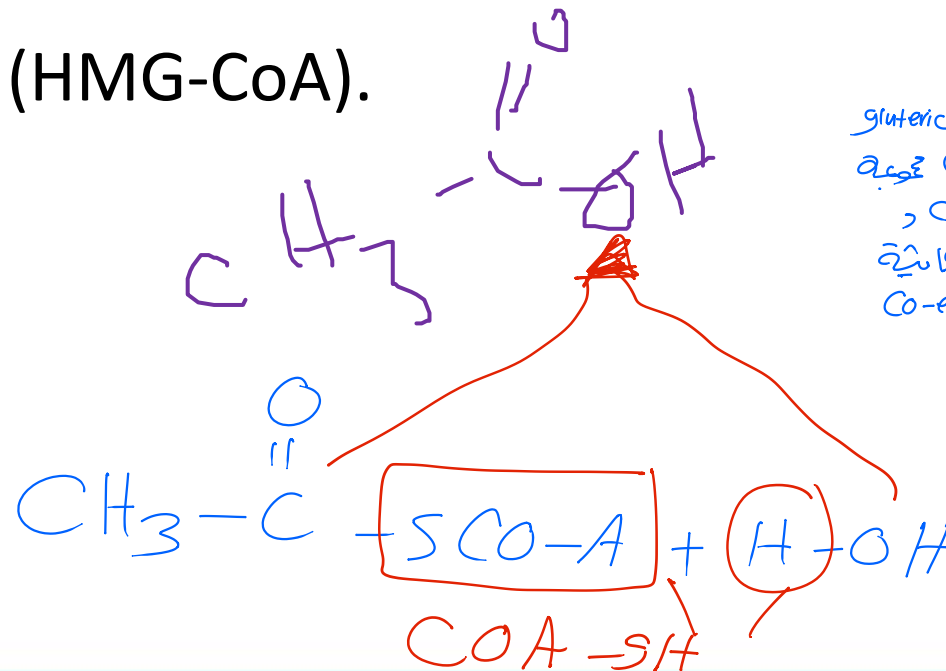
ketogenesis

The first step in the formation of acetoacetate, occurring in the liver, is the enzymatic condensation of two molecules of acetyl-CoA, catalyzed by thiolase; this is simply the reversal of the last step of β oxidation.



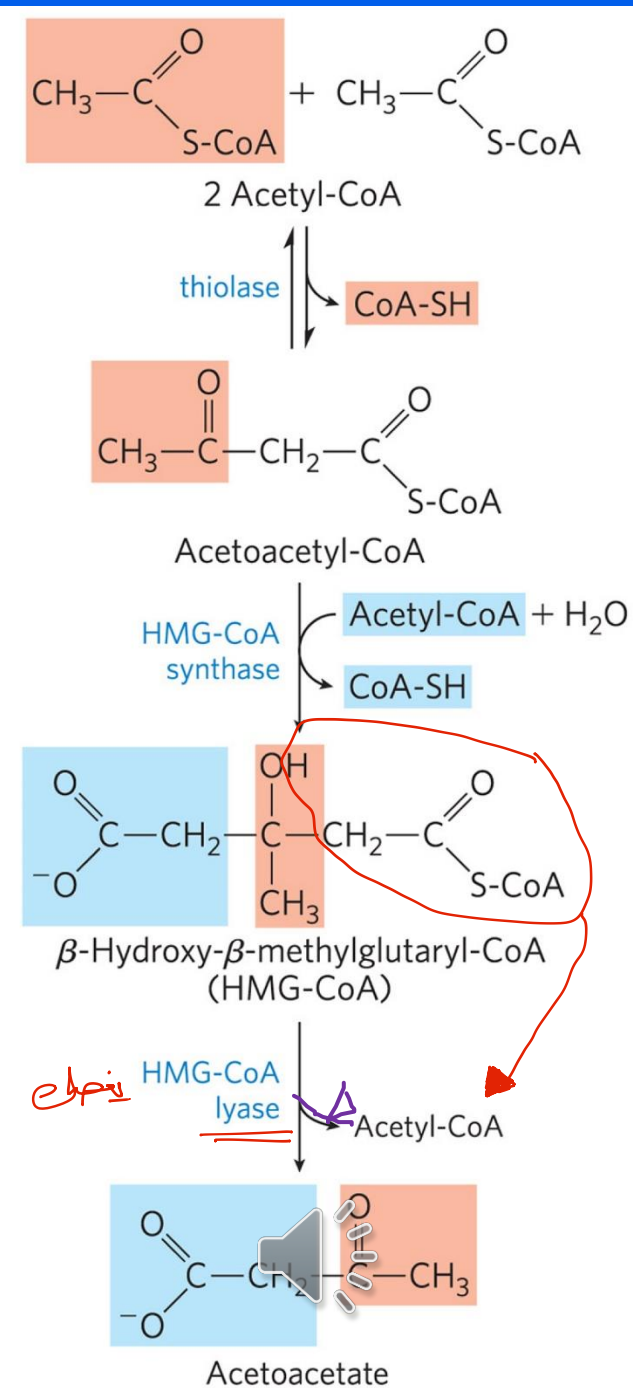
ketogenesis

The acetoacetyl-CoA then condenses with another molecule of acetyl-CoA to form β -hydroxy β -methylglutaryl-CoA (HMG-CoA).



ketogenesis

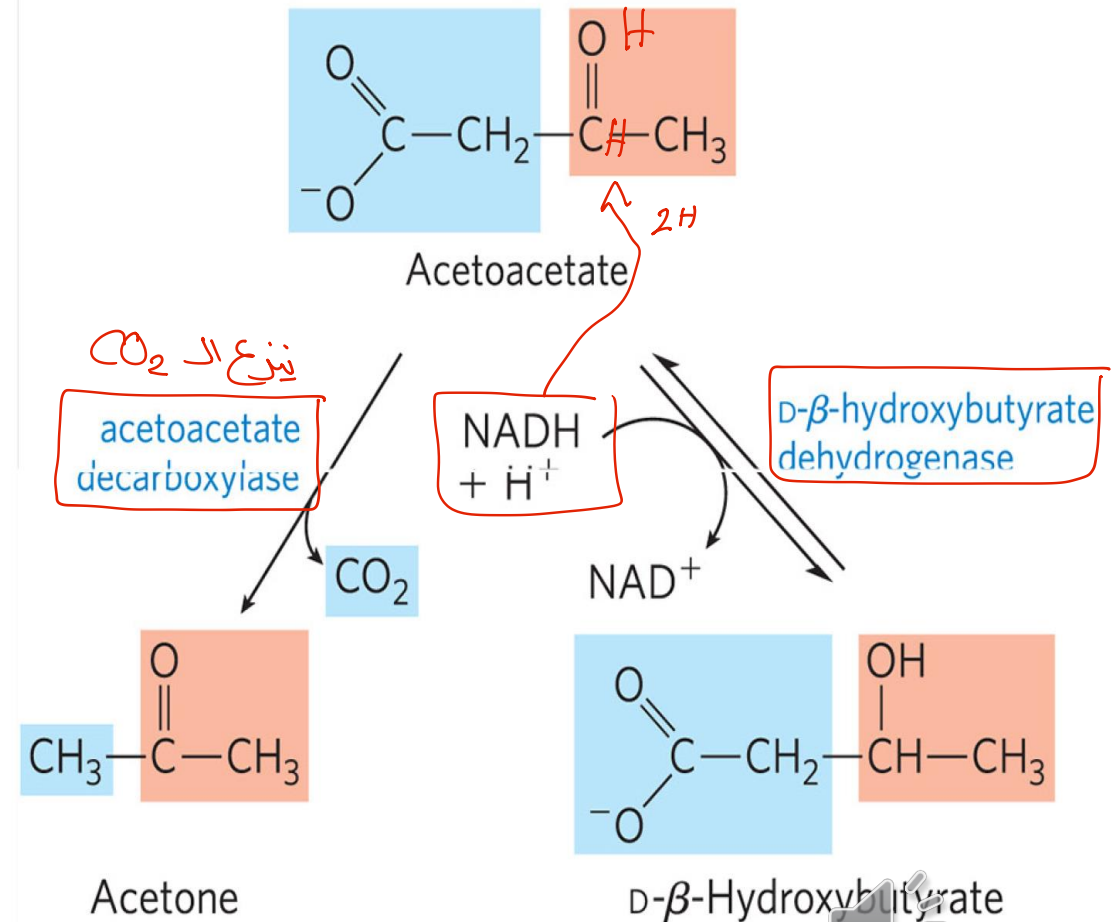
The HMG-CoA is cleaved to free acetoacetate and acetyl-CoA.



ketogenesis

Formation of β - hydroxybutyrate and acetone: Acetoacetate is either:

- a) decarboxylation into acetone.
- b) Reduced by hydroxybutyrate dehydrogenase into β -hydroxybutyrate.



Conditions that increase ketogenesis:

1. Starvation.

2. Diabetes mellitus.

→ lipolysis
رشح الدهون في خلايا ال

3. Low carbohydrate diet.

• Regulation of ketogenesis:

• After meal, ~~insulin~~ is secreted, and this ~~Inhibits~~ lipolysis and in turn ~~Inhibits~~ ketogenesis.

• During fasting anti-insulin hormones are secreted e.g. glucagon. This stimulates lipolysis and In turn ketogenesis.



OXIDATION OF KETONE BODIES (KETOLYSIS): Site:

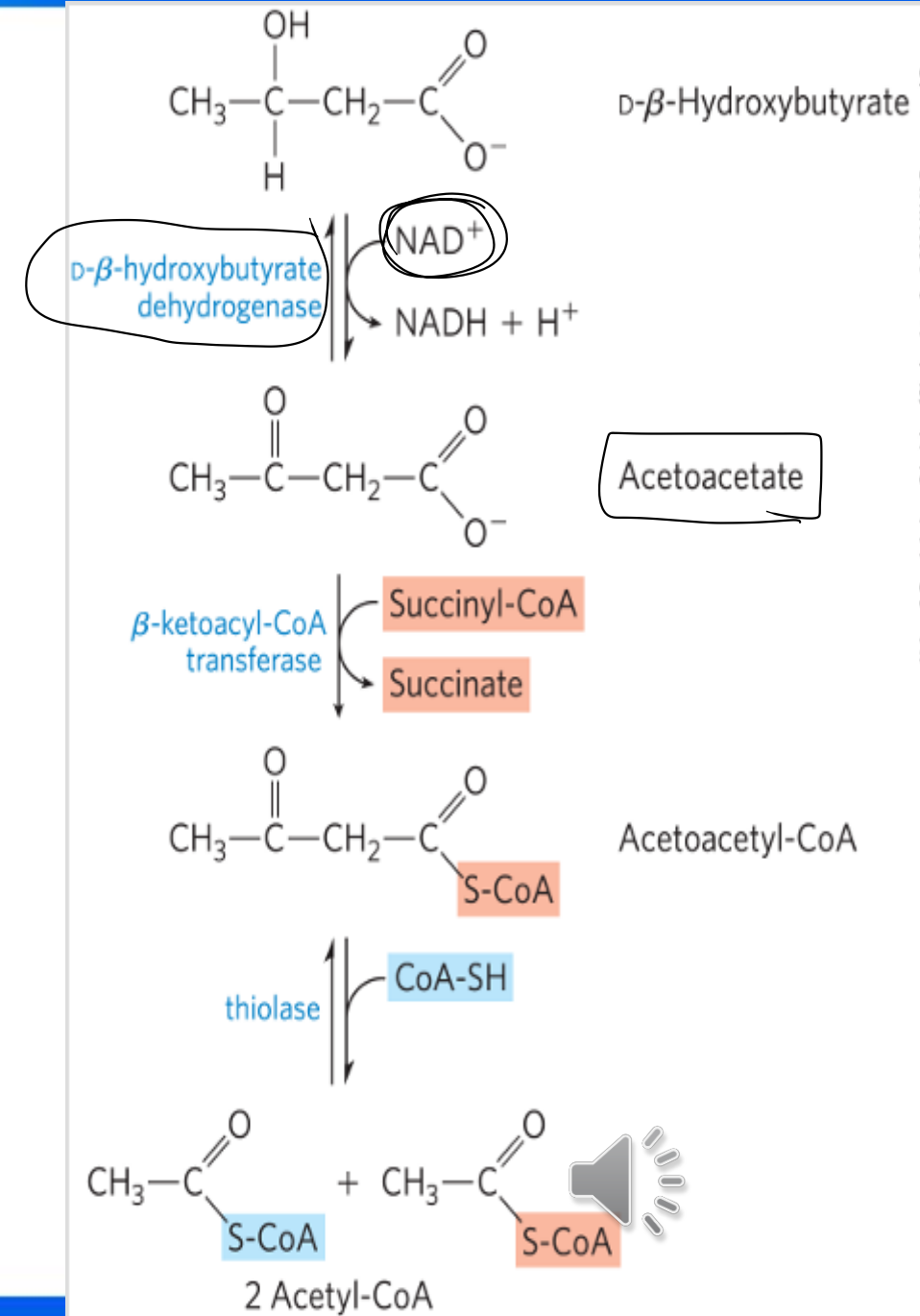
لا ينتقل إلى BBB
نريد استخدامه في الـ Brain حتى يحرر Ketone Bodies إلى Acetyl-CoA التي ما يقدر ليري الـ BBB واستخدمه الـ Brain في هذه الحالة
أجل إنتاج الطاقة ويطلع منه 12 ATP

- Intracellular location: Mitochondria
- Organ location: Extra hepatic tissues as muscles , Brain
- Note: Ketolysis does not occur in liver because it does not contain enzymes for it



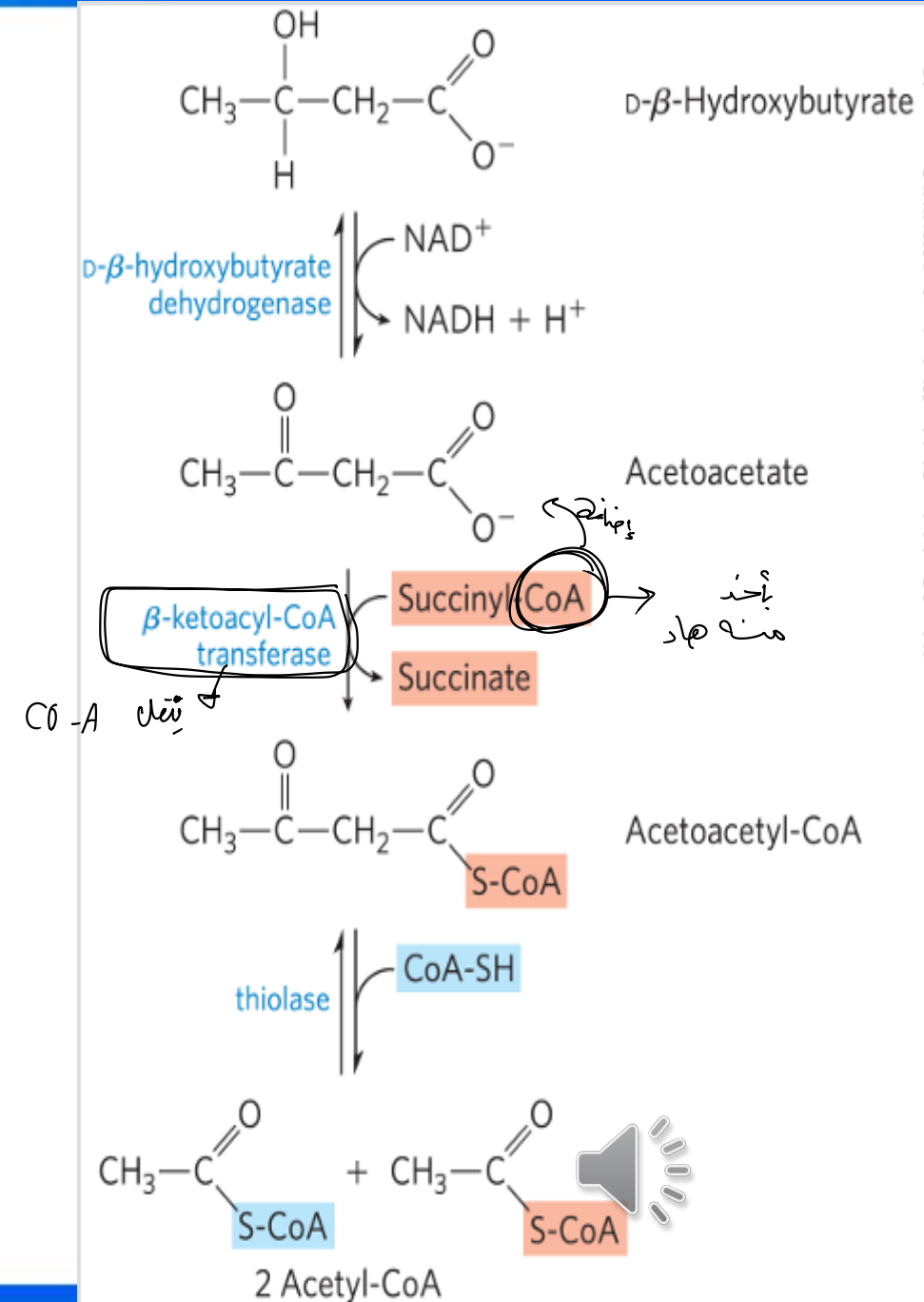
KETOLYSIS: Steps:

- Acetone is volatile and removed in the expired air.
- β -Hydroxybutyrate is converted in to acetoacetate by hydroxybutyrate dehydrogenase enzyme.



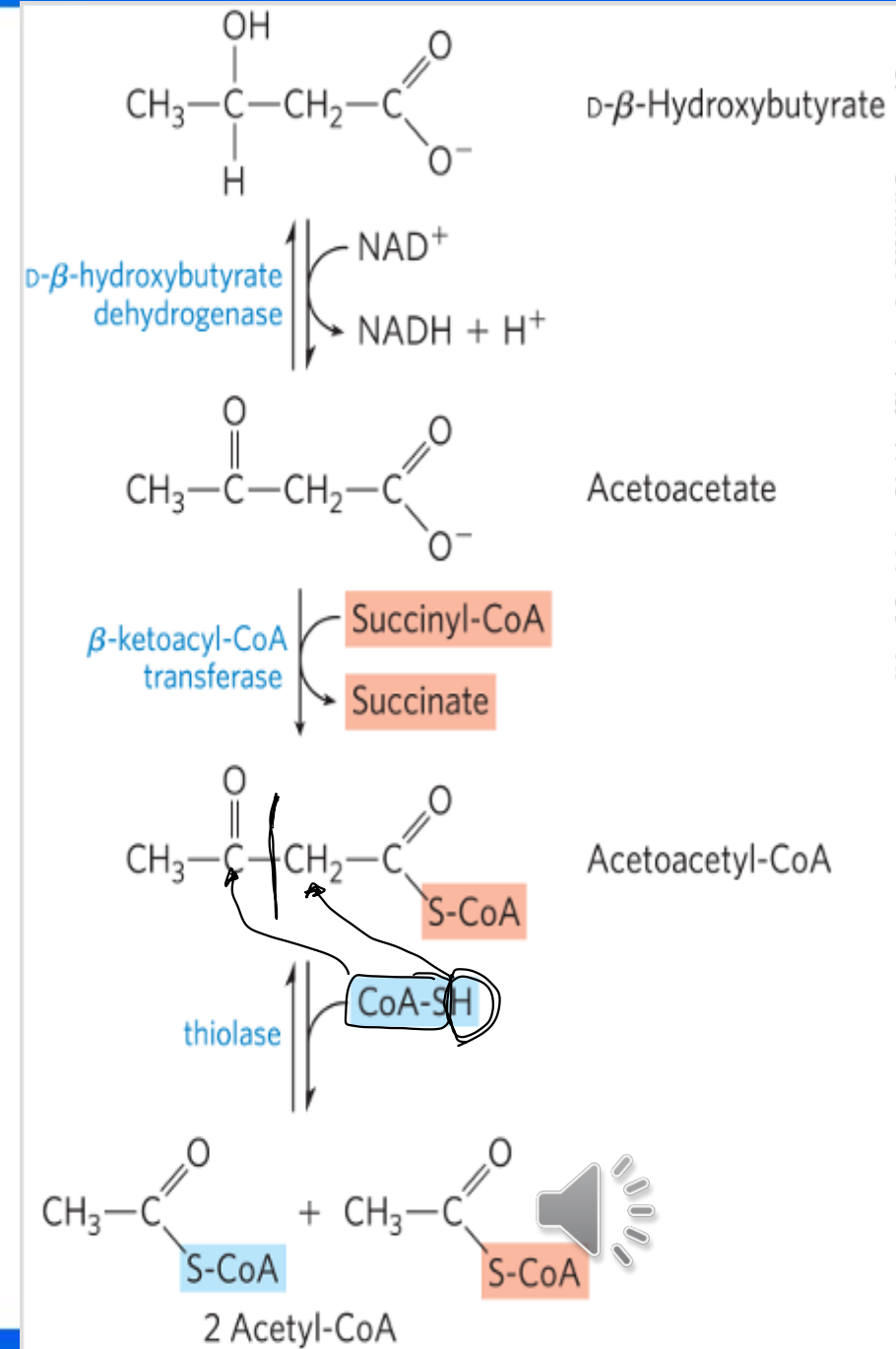
KETOLYSIS: Steps:

- Acetoacetate is then activated into acetoacetyl-CoA by in the presence of succinyl-CoA



KETOLYSIS: Steps:

- Acetoacetyl CoA is split into two molecules of acetyl CoA which are oxidized in citric acid cycle; Each gives 12 ATP



Thanks



Medical Biochemistry
Lipid Metabolism

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

Al-Azhar University-Gaza



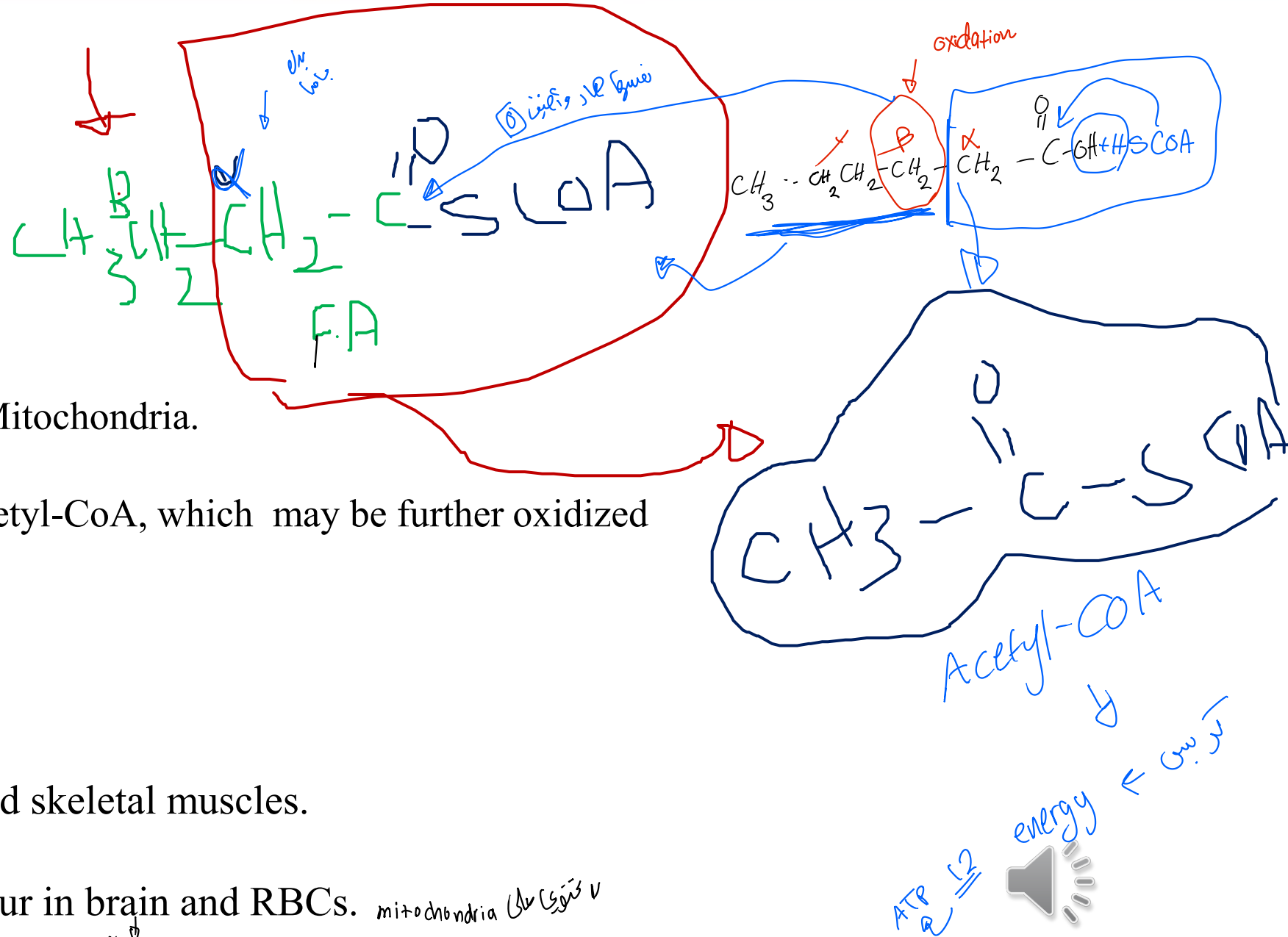
Fatty acids oxidation

Among the different foodstuffs, lipids give (through fatty acids oxidation) the maximum amount of energy. 3
Different pathways for fatty acid oxidation are present: α , β and ω .



β-Oxidation

- Site:
 - Intracellular location: Mitochondria.
 - FA. Are oxidized to acetyl-CoA, which may be further oxidized completely in the TCA
 - Organ location:
 - Liver, kidney, heart and skeletal muscles.
 - β -Oxidation never occur in brain and RBCs. mitochondria

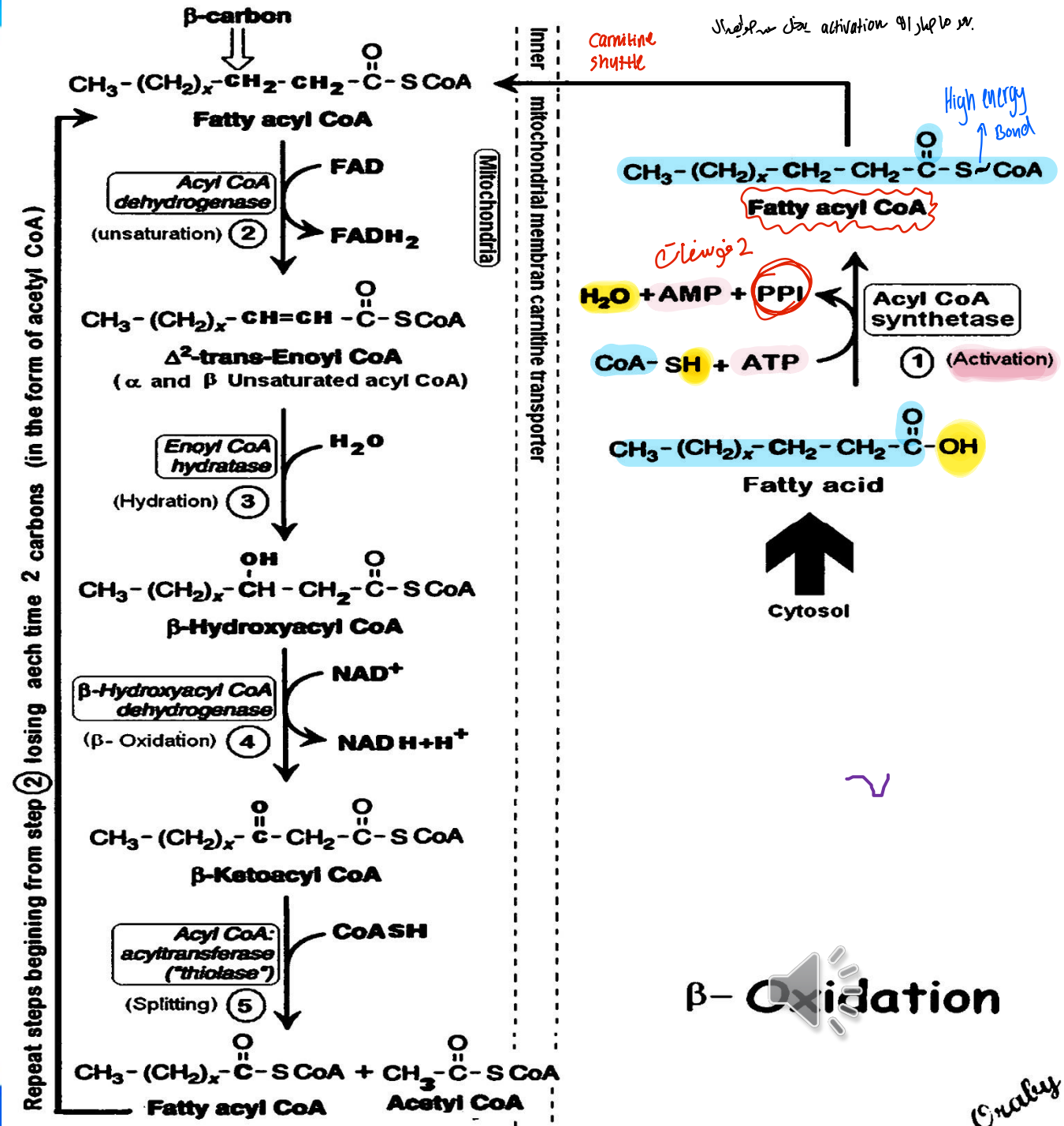


β-Oxidation steps

1. Activation of fatty acid and transport inside the mitochondria:

A. Catalyzed by fatty acyl CoA synthetase enzyme and carnitine shuttle.

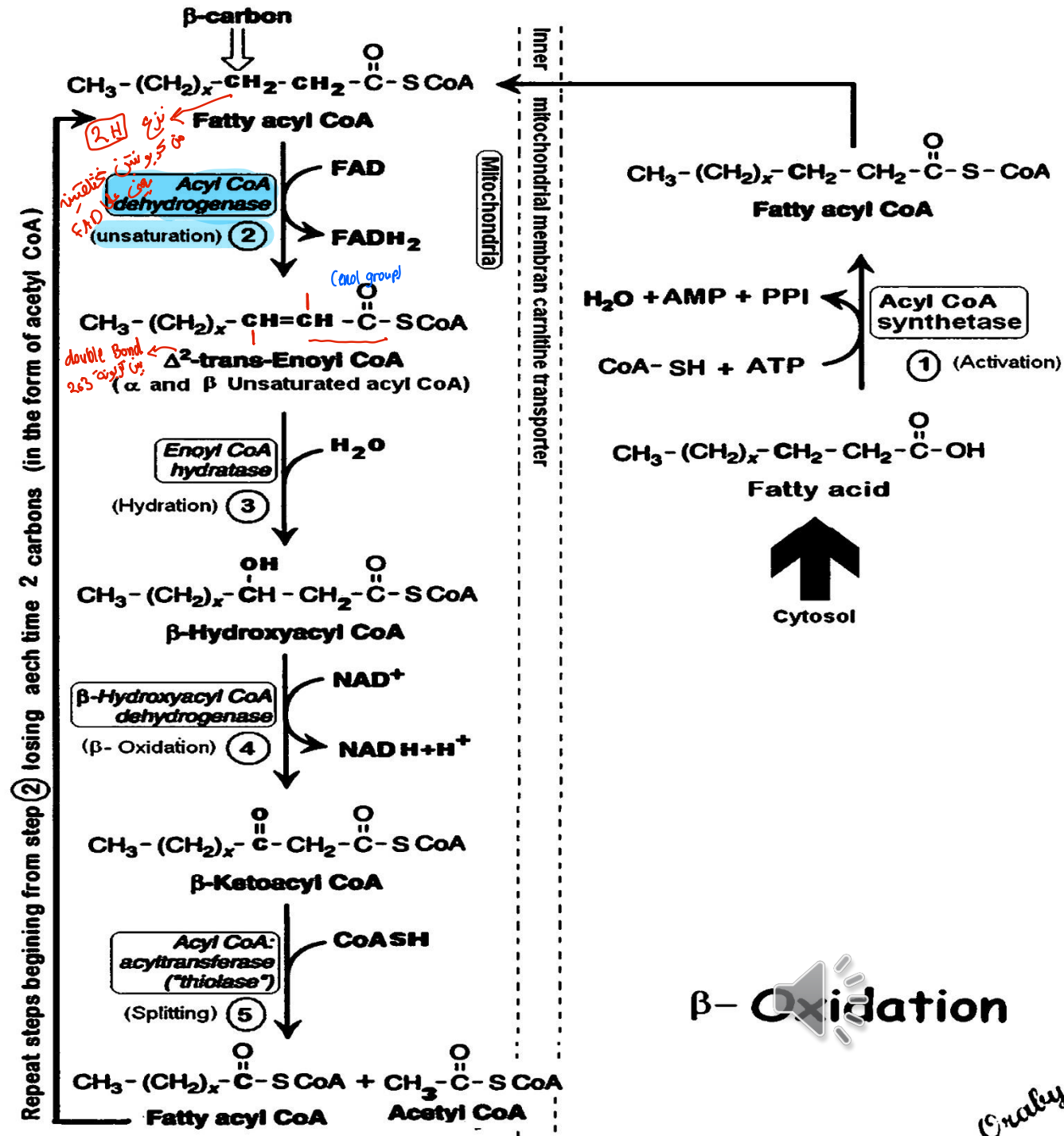
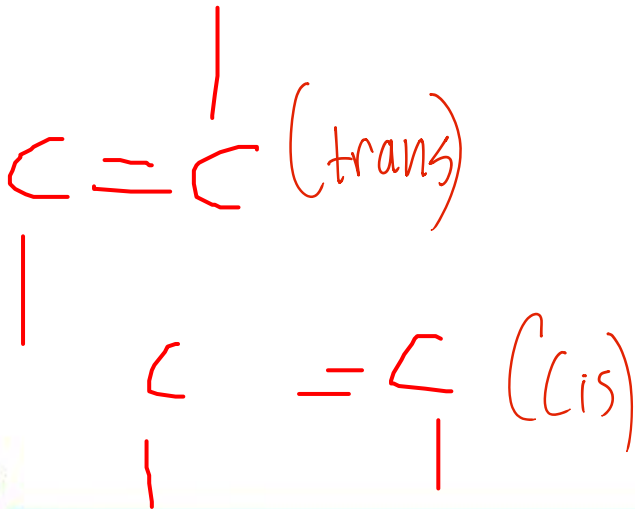
B. 2 high energy bonds are utilized:



β-Oxidation steps

2- Unsaturation of fatty acids:

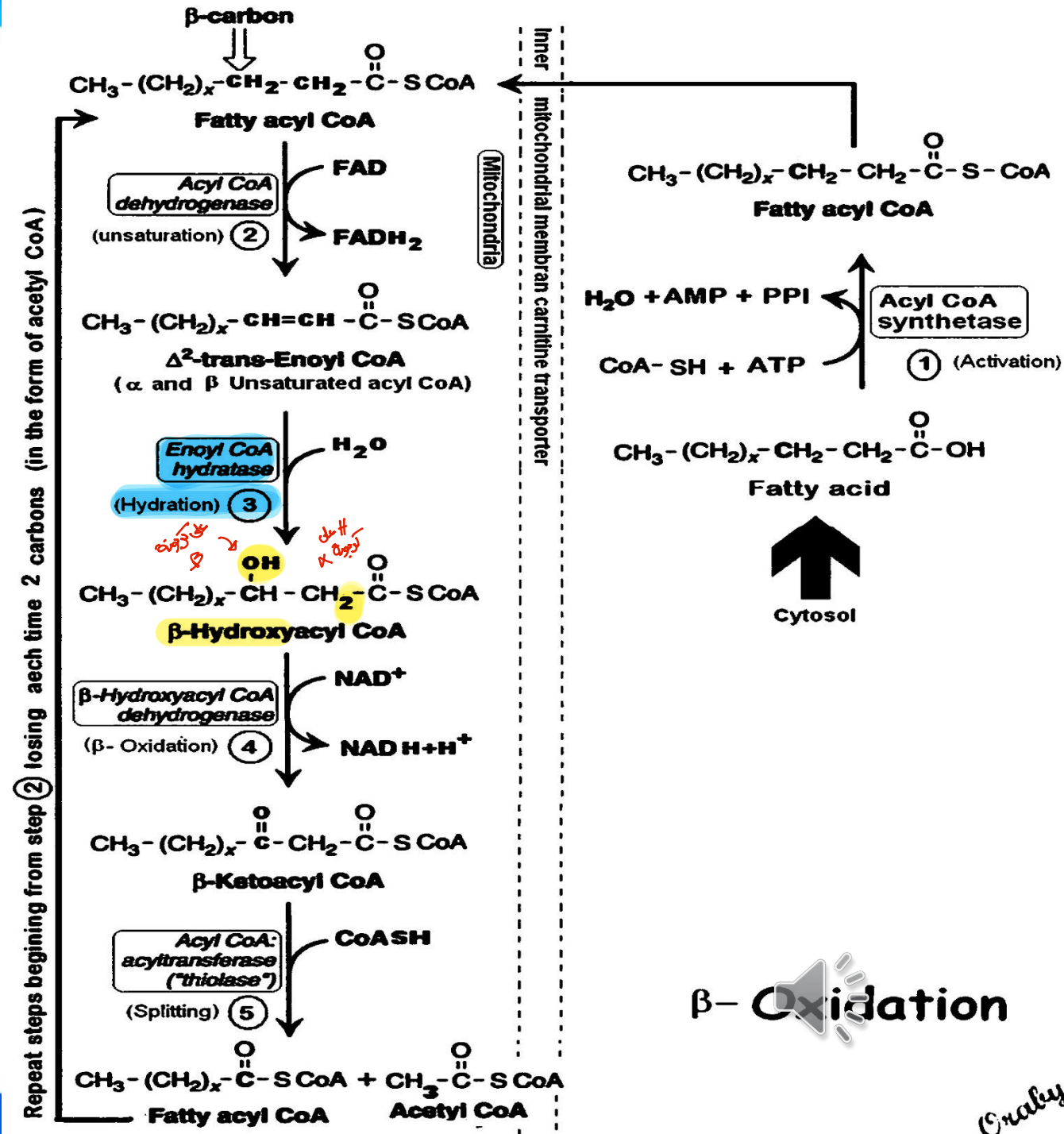
- Catalyzed by fatty acyl CoA dehydrogenase enzyme .
- This enzyme is one of flavoproteins and its reduced coenzyme (FADH_2) gives 2 ATP when oxidized in the respiratory chain.



β-Oxidation steps

3. Hydration :

- A. Catalyzed by enoyl CoA hydratase enzyme.
- B. It helps the addition of water to **saturate double bonds**.

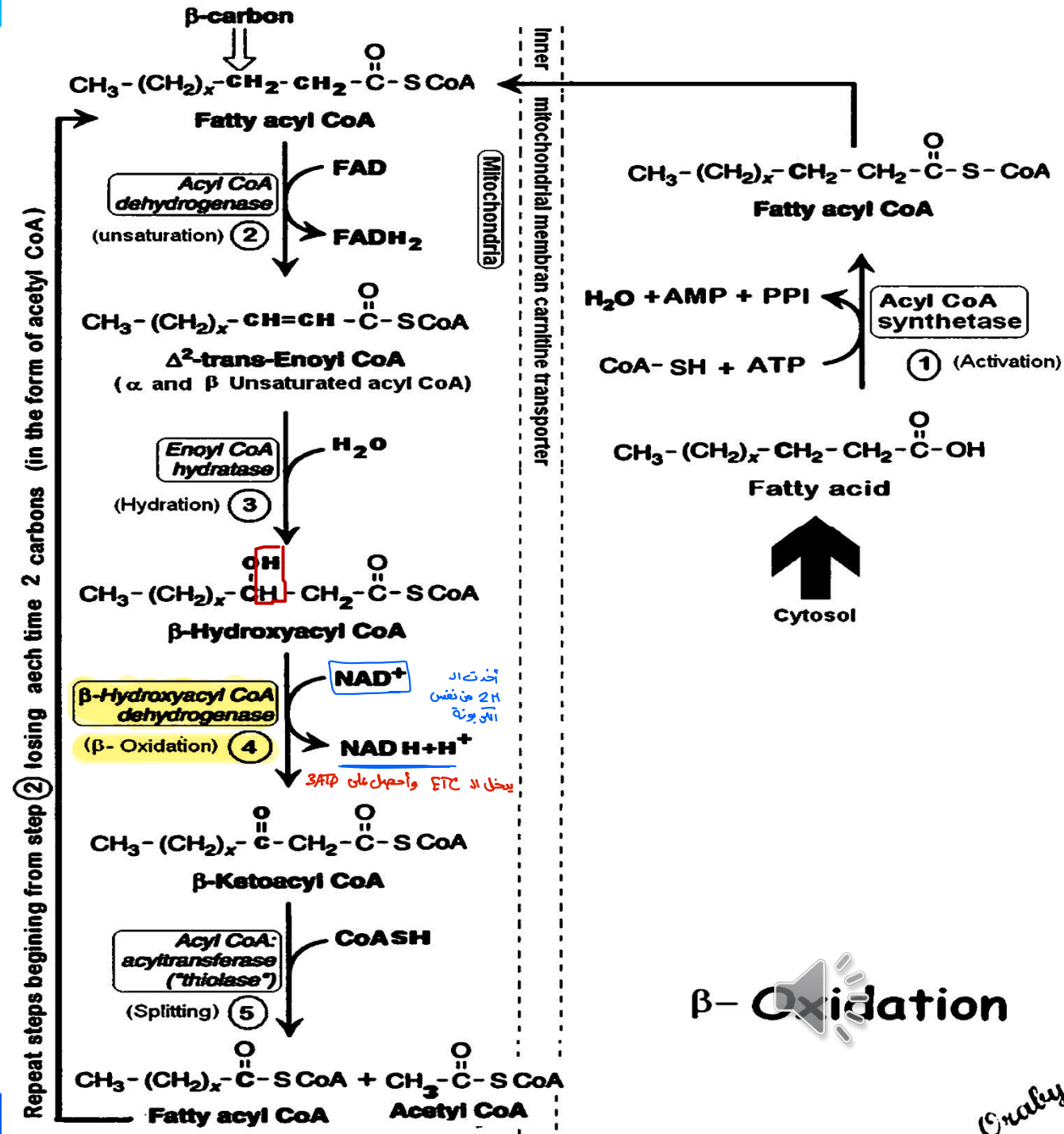


β-Oxidation steps

4. Oxidation:

Catalyzed by β-hydroxyacyl CoA dehydrogenase enzyme.

Its reduced coenzyme (NADH+H⁺) gives 3 ATP when oxidized in the respiratory chain.



β-Oxidation

Crabby

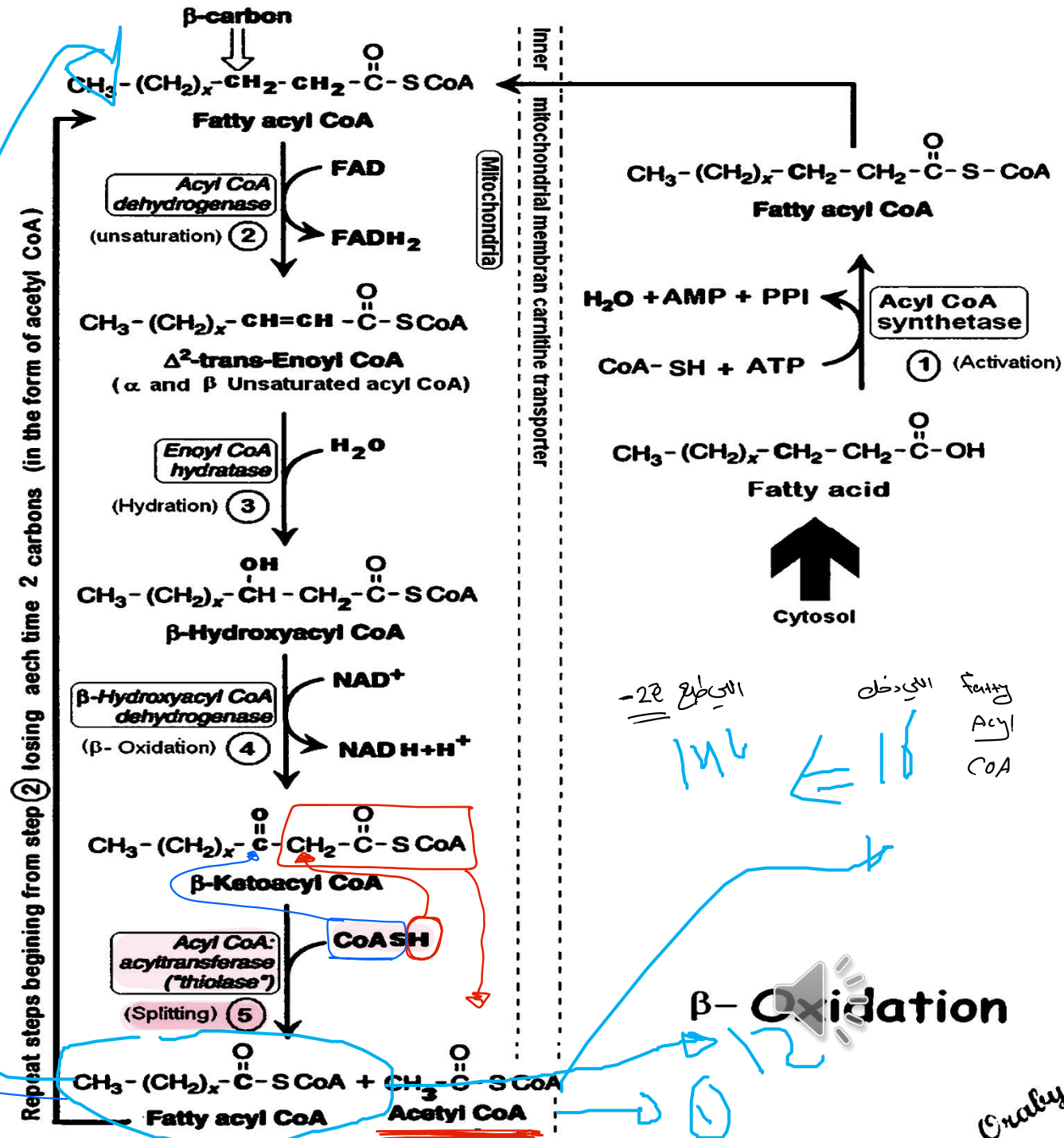
β-Oxidation steps

5. Splitting (cleavage) step:

Catalyzed by thiolase enzyme.

It splits β-hydroxyacyl CoA into acetyl CoA and acyl CoA (shorter than the original one by 2 carbon atoms).

يجب الخطوة الأولى
على سطح يفرغ Acetyl CoA



تم الدراسة بتاريخ 4.8.2025
يوم الاثنين الساعة 9: 54 ليلاً
والناس ينتج من المنطقة
والقذائف بغيرها من فوسفه البنية
والصباحين تلك مكانه والقصص
وصوت الإضافة فيد لفرع دخول
لمنطقة نعم، إنه جنوب الاستمرارية
الهدوب من الماء إلى داخل بئر أقل
سوى.

Energy production of β -oxidation:

β -oxidation of palmitic acid will be repeated 7 times (turns) to produce 8 acetyl CoA.

In each turn, one molecule of reduced FADH_2 and one molecule of reduced $\text{NADH} + \text{H}^+$ are produced.

They are oxidized in respiratory chain to give 5 ATP.

FADH_2 gives 2 ATP

$\text{NADH} + \text{H}^+$ gives 3 ATP

7 turns $\times$ 5 ATP = 35 ATP.

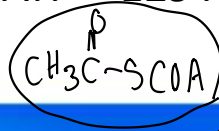
Oxidation of one molecule of acetyl CoA in Krebs' cycle gives 12 ATP.

8 Acetyl CoA $\times$ 12 ATP = 96 ATP

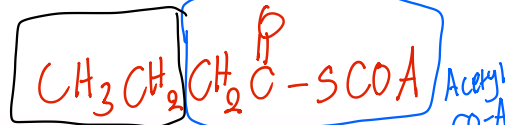
Two high energy phosphate bonds are utilized in the first reaction (catalyzed by acyl CoA synthetase) which occurs for one time only.

Net energy gain = Energy produced - Energy utilized = (35 ATP + 96 ATP) - 2 ATP = 131 ATP - 2 ATP = 129 ATP

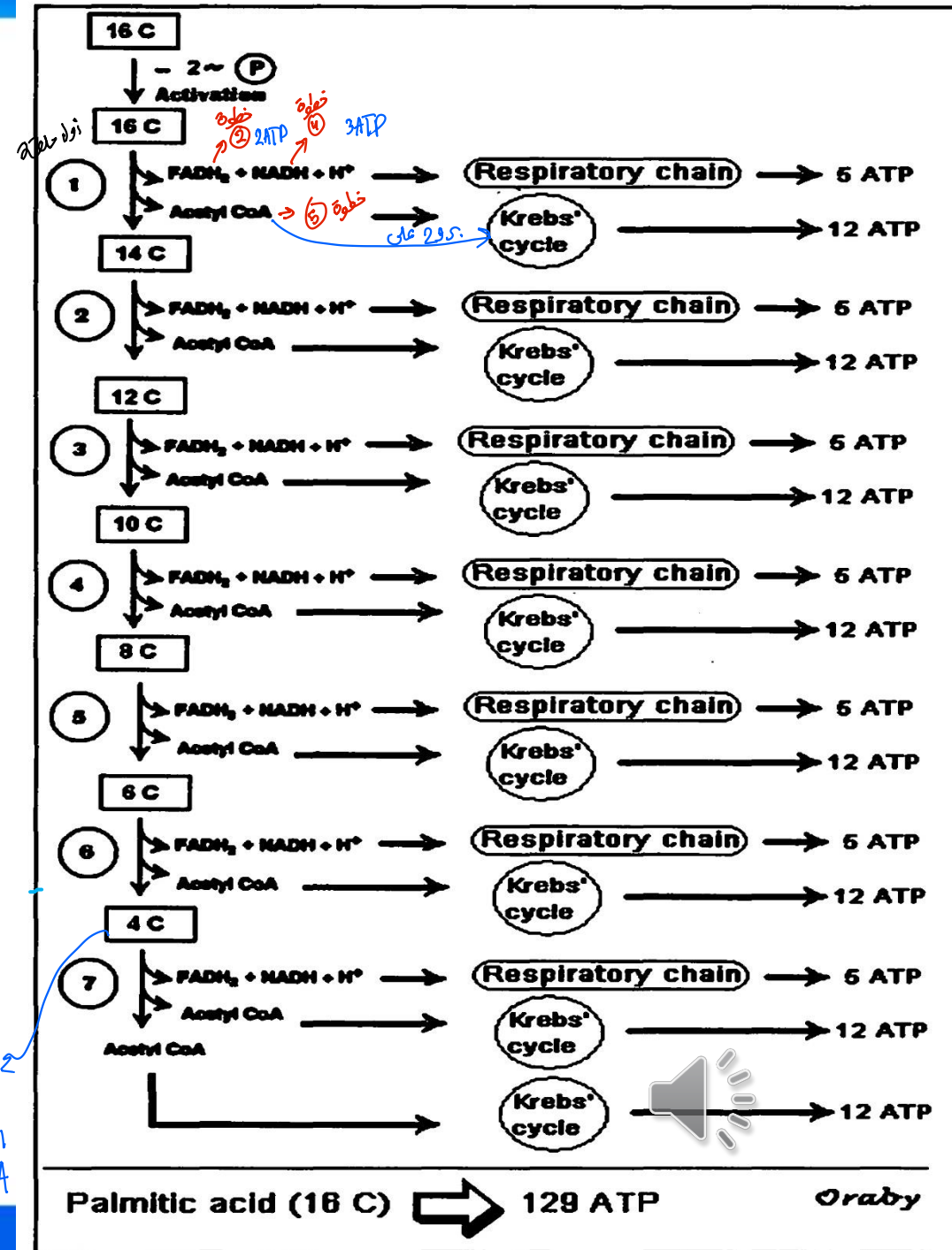
M. ELEYAN



Acetyl CoA



Acetyl CoA



Energy production of β -oxidation:

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They are oxidized in respiratory chain to give 5 ATP.

FADH_2 gives 2 ATP

$\text{NADH} + \text{H}^+$ gives 3 ATP

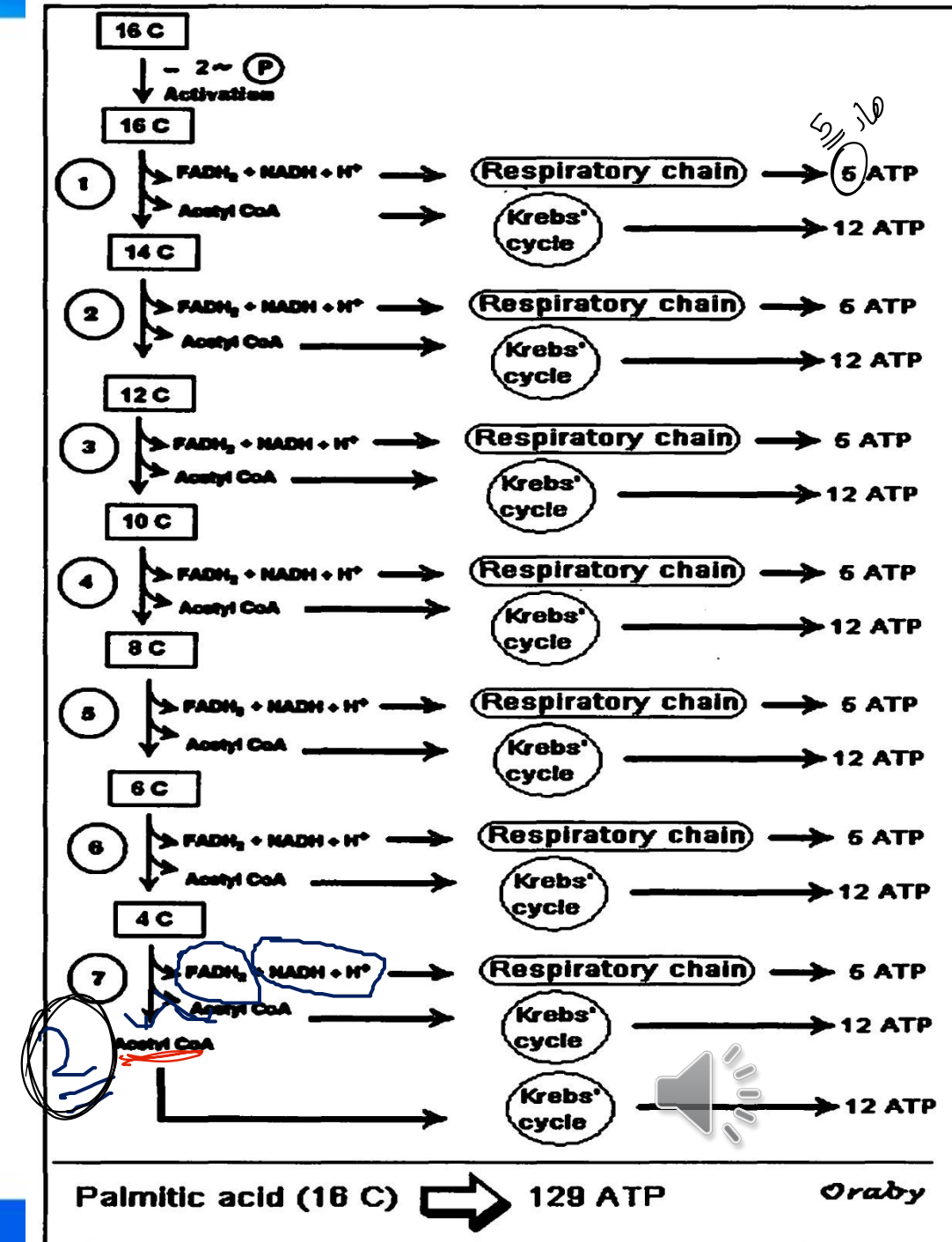
7 turns $\times$ 5 ATP = 35 ATP.

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Net energy gain = Energy produced - Energy utilized = (35 ATP + 96 ATP) - 2 ATP = 131 ATP - 2 ATP = 129 ATP



Energy production of β -oxidation:

(للمر الزوجي)

- Calculation formula of energy production of oxidation of any fatty acid:

$$\text{Palmitic} = 16 \rightarrow \text{7} \quad \text{35} \quad \text{131} \quad \text{8} \times 12 = 96 \quad - 2 \text{ ATP} = 129$$

$$= \left[\left(\frac{N}{2} - 1 \right) \times 5 \text{ ATP} \right] + \left[\frac{N}{2} \times 12 \text{ ATP} \right] - 2 \text{ ATP}$$

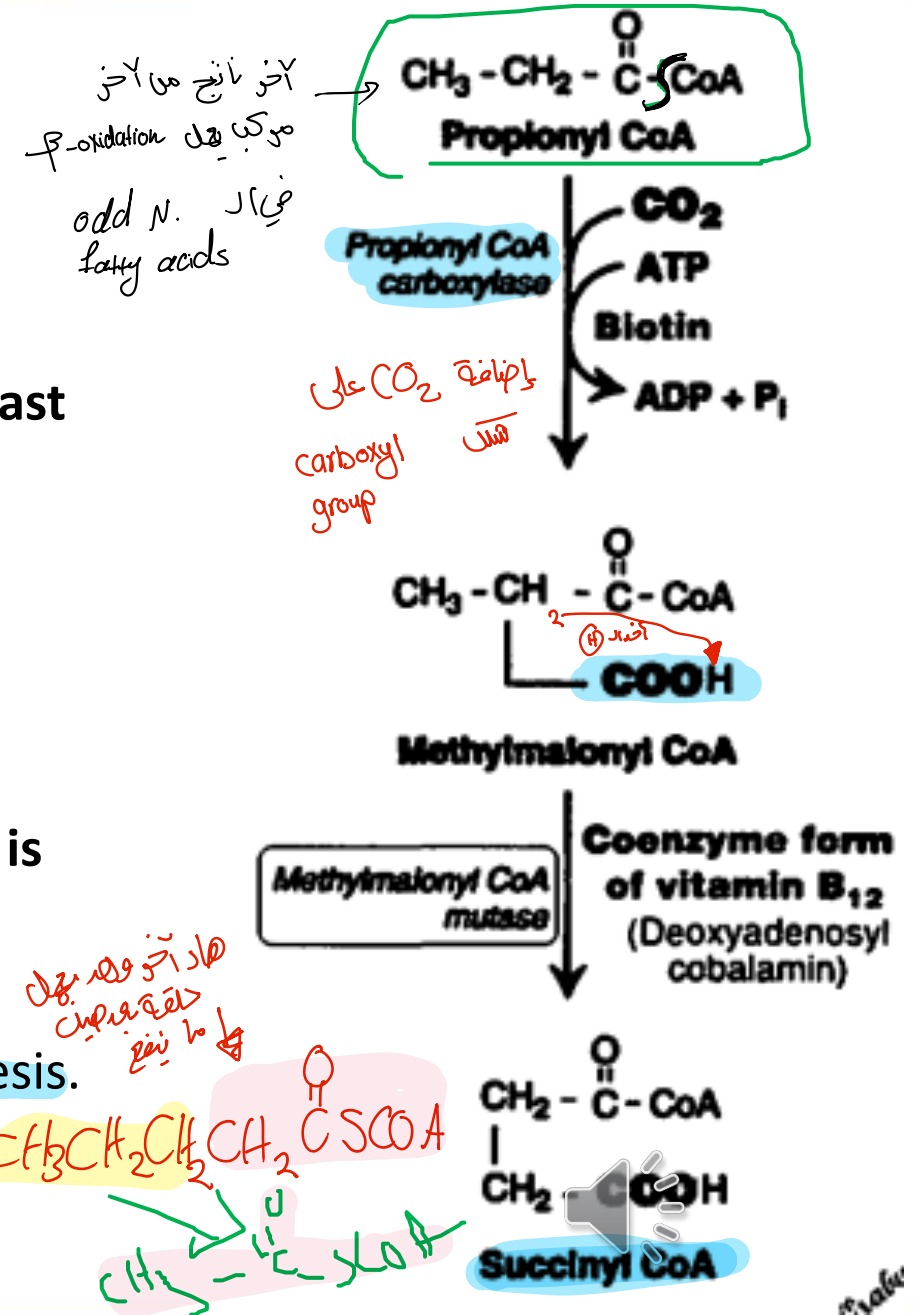
- Where N = Number of carbons of fatty acid

$$N=22 \quad \left[\left(\frac{22}{2} - 1 \right) \times 5 \text{ ATP} \right] + \left[\frac{22}{2} \times 12 \text{ ATP} \right] - 2 \text{ ATP} = 180 \text{ ATP}$$



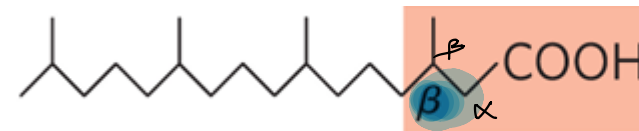
β-oxidation of odd number fatty acids:

- They are oxidized by β-oxidation for multiple cycles till the last Three carbons (a propionyl CoA) is produced.
- Then propionyl CoA is converted to succinyl CoA in the following steps:
- propionyl CoA is carboxylated to methylmalonyl-CoA which is converted to succinyl-CoA ; mutase needs B12 as coenzyme
- Fate: 1) Glucose synthesis (gluconeogenesis). 2) Heme synthesis. 3) Oxidation in citric acid cycle.



α -Oxidation

- A. This type of oxidation occurs in α position
- It is a mechanism mainly for oxidation of branched chain fatty acid, which are methylated at β position.
- It is specific for oxidation of phytanic acid, a long-chain fatty acid (3, 7, 11, 15 tetramethylpalmitic acid), is derived from the phytol side chain of chlorophyll. يعني هو موجود في سبائك



Phytanic acid



α -Oxidation

- The presence of a methyl group on the β carbon of this fatty acid prevents the formation of a β -keto intermediate, making its β oxidation impossible. Humans obtain phytanic acid in the diet, primarily from dairy products and from the fats of ruminant animals; microorganisms in the rumen of these animals produce phytanic acid as they digest plant chlorophyll.

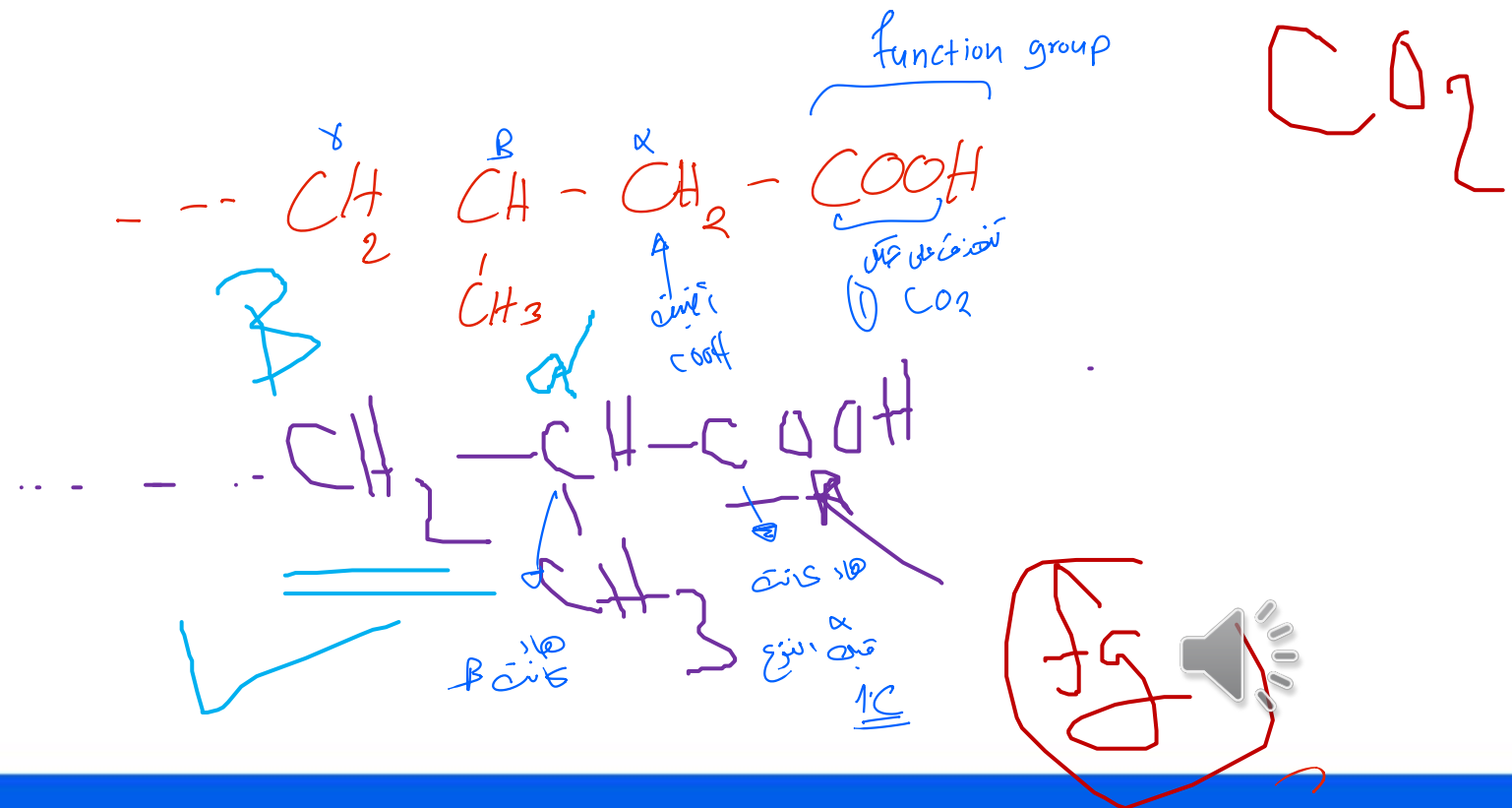
الحيوانات التي تأكل العشب

موضح



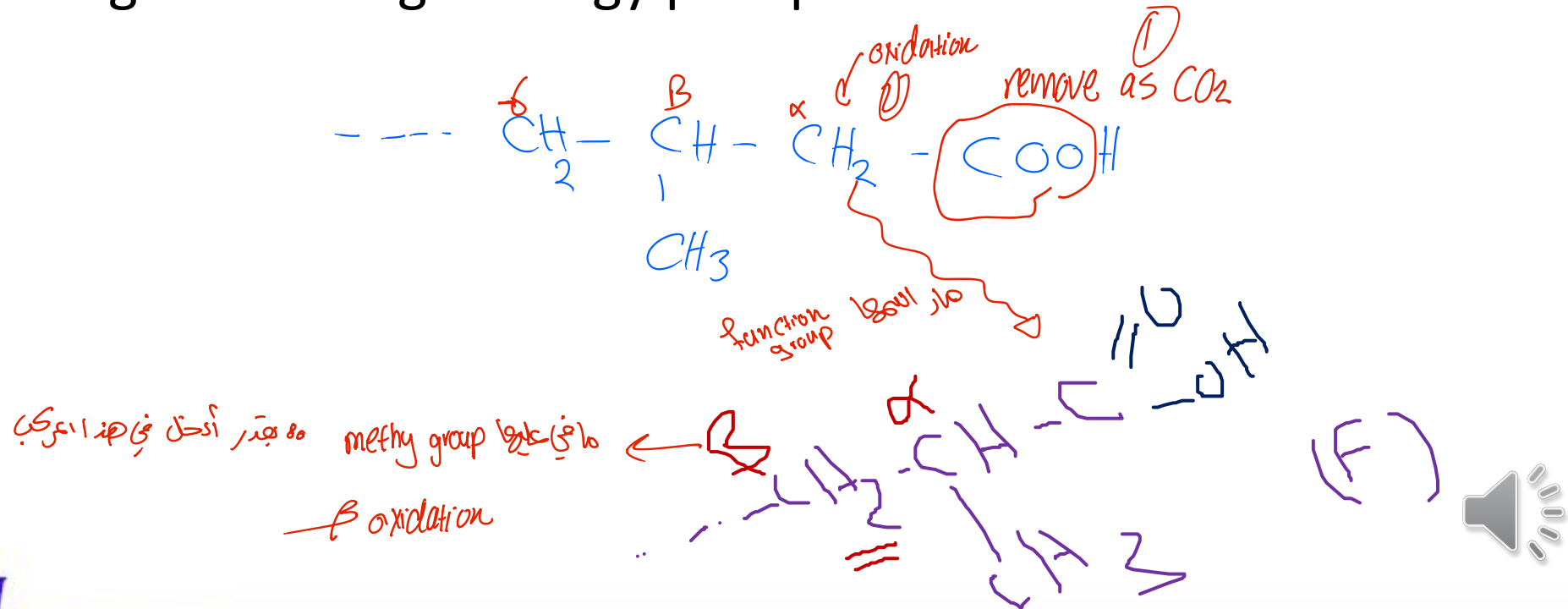
α -Oxidation

- In α -oxidation, there is one carbon atom removed at a time.
- It does not require CoASH and does not generate high energy phosphate.

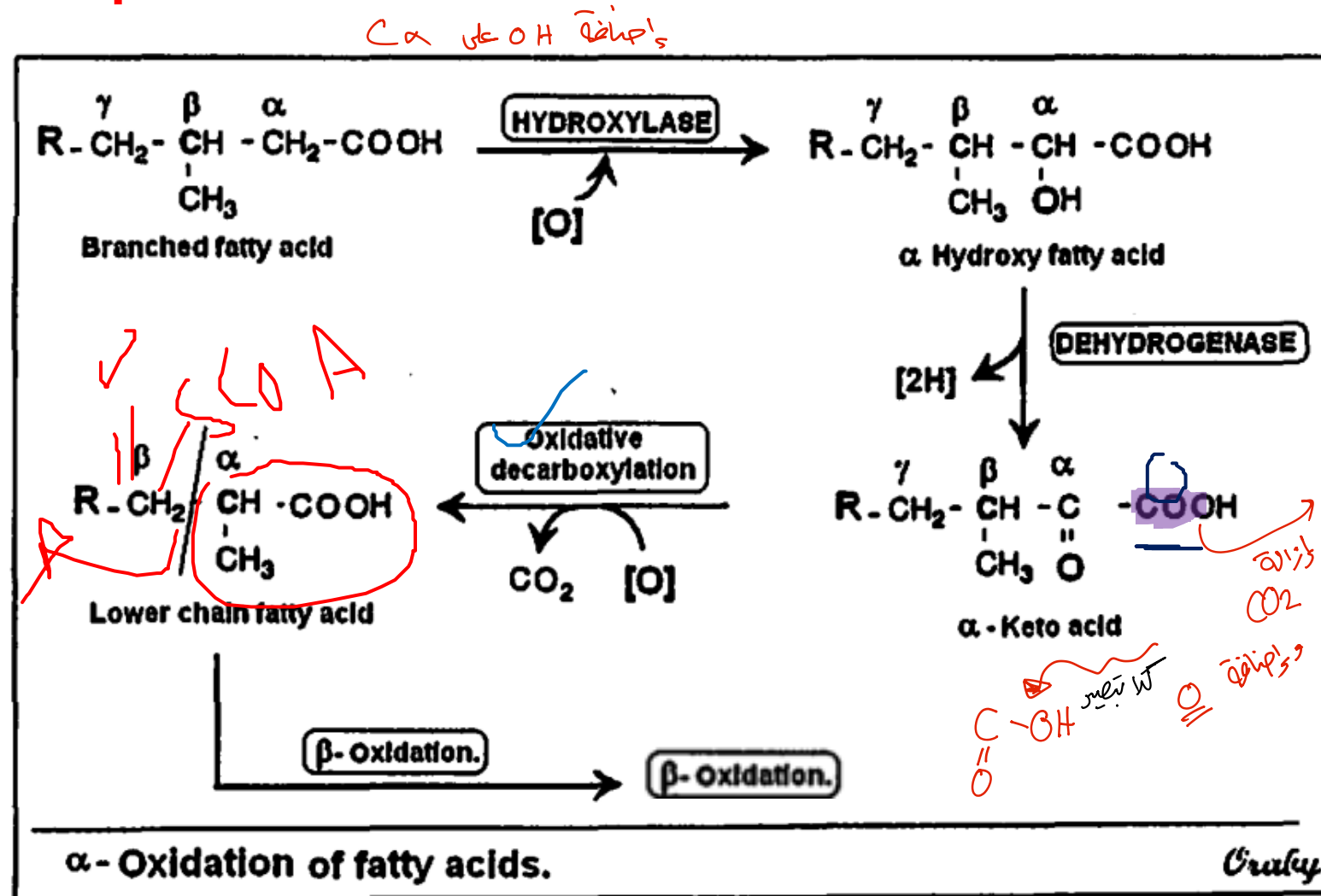


α -Oxidation

- In α -oxidation, there is one carbon atom removed at a time.
- It does not generate high energy phosphate.



α -Oxidation Steps:



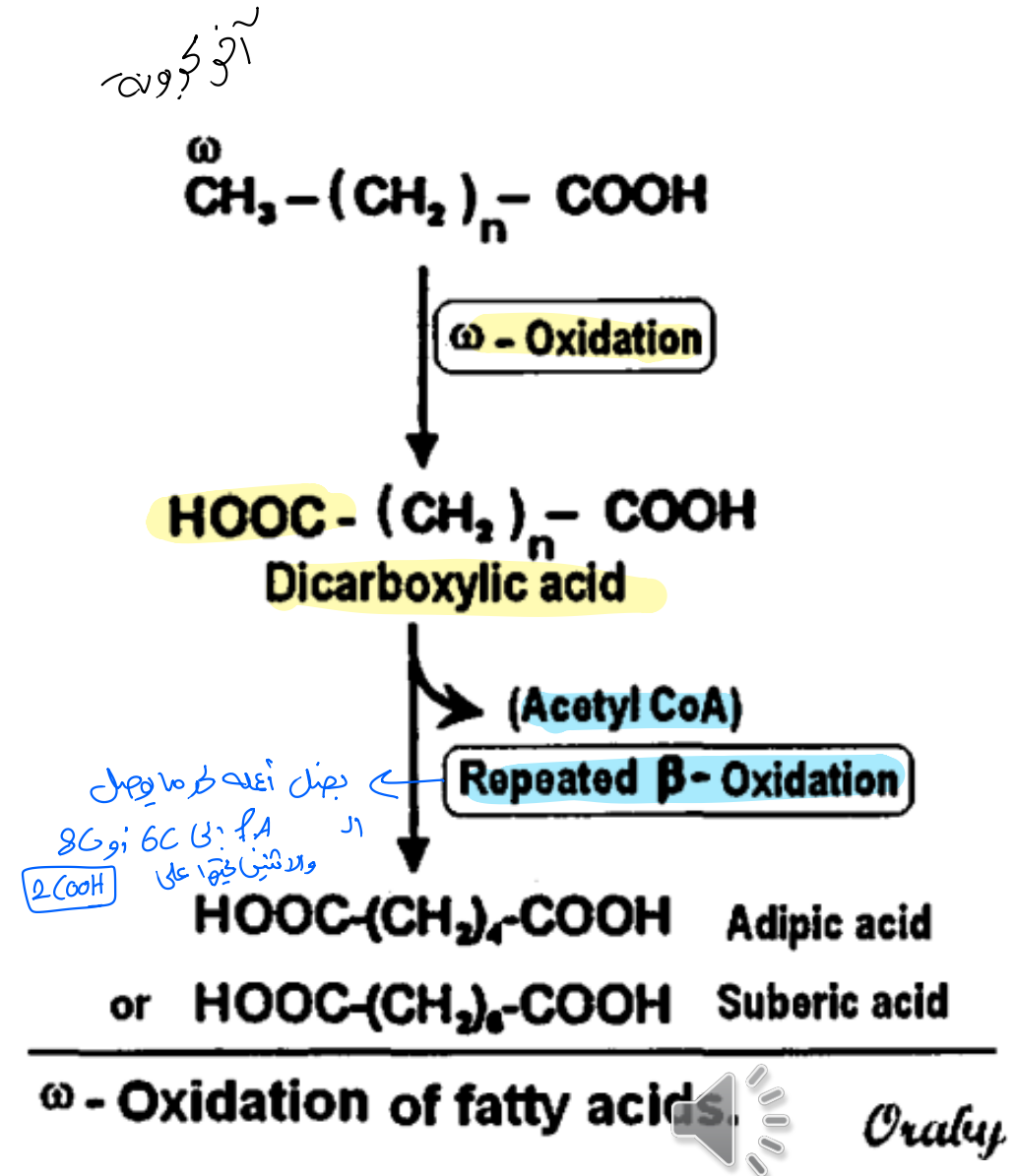
Refsum's disease:

- Refsum disease, resulting from a genetic defect in the enzymes responsible for α oxidation of phytanic acid (hydroxylase), leads to the accumulation of very high blood levels of phytanic acid, causing (by unknown mechanisms) severe neurological deficits, including blindness and deafness.



ω-Oxidation

- It is oxidation of terminal CH₃ group ((ω) carbon) of fatty acid.
- This produces dicarboxylic fatty acids. By β oxidation they are converted to adipic acid (6 carbons) and suberic acid (8 carbons).
- ω-Oxidation is a minor pathway for fatty acid oxidation and catalyzed by hydroxylase enzymes of cytochrome P450.



Ω-Oxidation

- The primary products of omega oxidation are **dicarboxylic acids**, such as adipic acid and suberic acid.
- These acids can be further metabolized to produce acetyl-CoA, which can enter the citric acid cycle for energy production.



ω-Oxidation

- Adipic and suberic acids are among the major products of omega oxidation.
- Elevated levels of these dicarboxylic acids in the blood or urine can be indicative of impaired beta-oxidation or other metabolic disorders.

carntine وجود - فشل
ETC في



Role of Omega Oxidation

دورهٔ اکسیداسیون آلفا-اکسیداسیون

- Omega oxidation becomes more prominent when beta-oxidation is impaired, such as in conditions of mitochondrial dysfunction or carnitine deficiency.
در شرایط اختلال عملکرد میتوکندری یا کمبود کarnitine

- It can also be activated during fasting or low-carbohydrate diets.

↑ lipolysis



Thanks

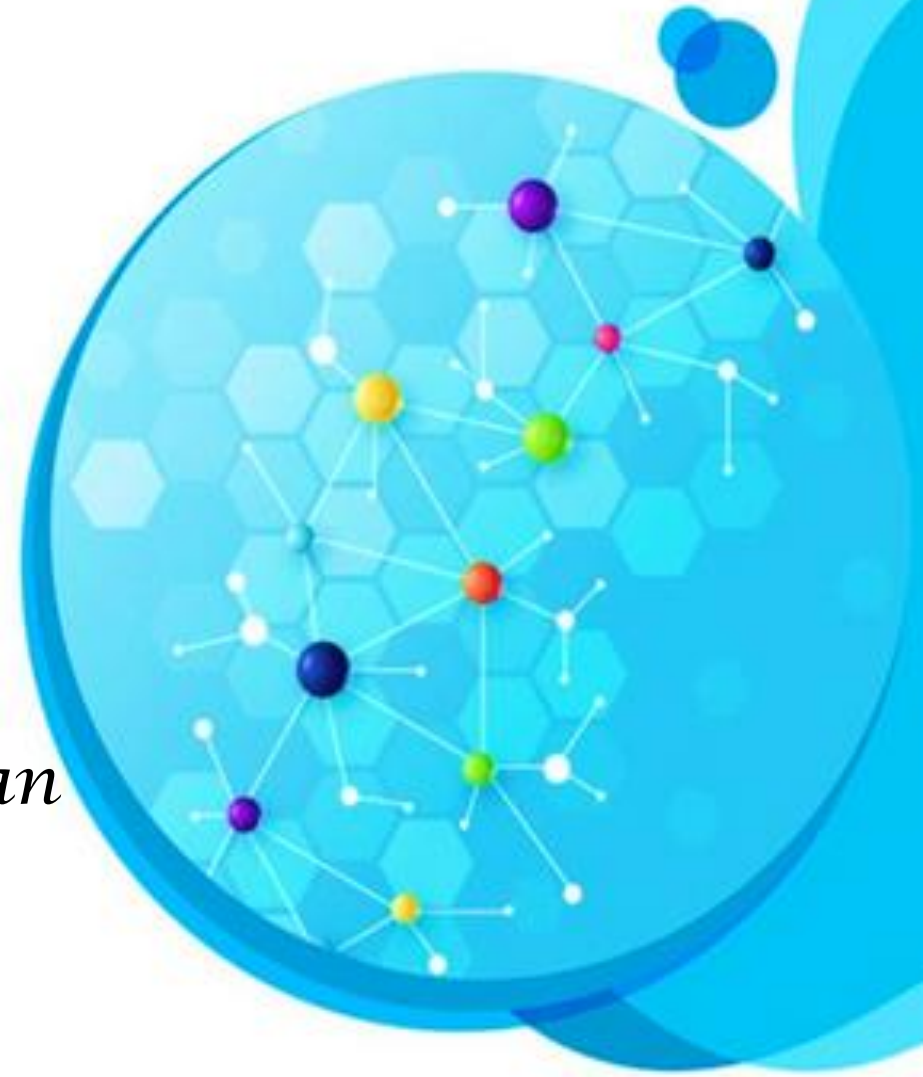
Medical Biochemistry

Protein Metabolism

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

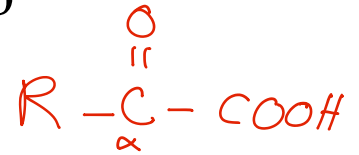
Al-Azhar University-Gaza



General catabolic pathways of amino acids



- Most catabolic reactions are preceded by cleavage of the amino acids into ammonia and the carbon skeleton (usually in the form of an α -keto acid).
urea cycle 11
- The ammonia is mostly converted to urea, which is excreted in urine.
- Little ammonia is also excreted in urine.
- The carbon skeleton may be converted to glucose or ketone bodies, or may be oxidized to carbon dioxide and water.



General catabolic pathways of amino acids

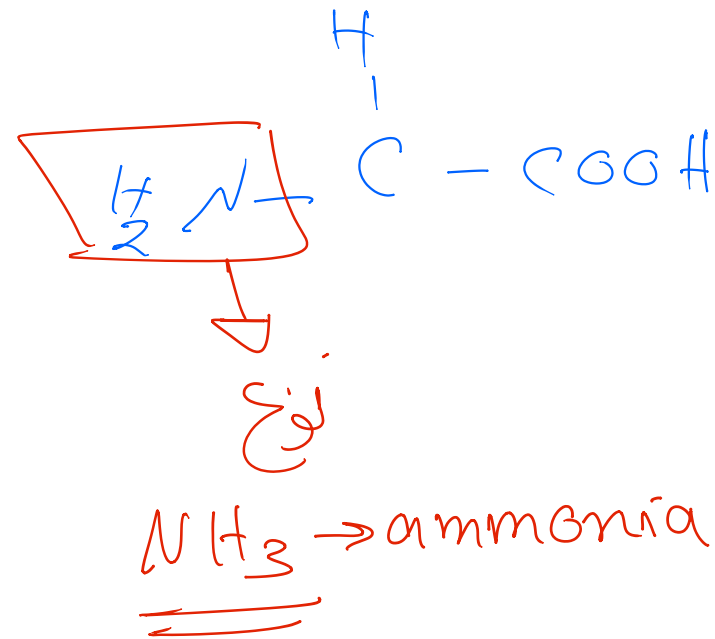
1. Transamination.
2. Deamination
3. Transdeamination
4. Decarboxylation.

General catabolic pathways of amino acids

- **Deamination:**
 1. Oxidative deamination.
 2. Non-oxidative deamination.
 3. Hydrolytic deamination.

Deamination:

- Definition: It is the removal of amino group from amino acids in the form of ammonia (NH_3).
- Site: Mostly liver and kidney.
- Types:
 - Oxidative deamination.
 - Non-oxidative deamination.
 - Hydrolytic deamination:



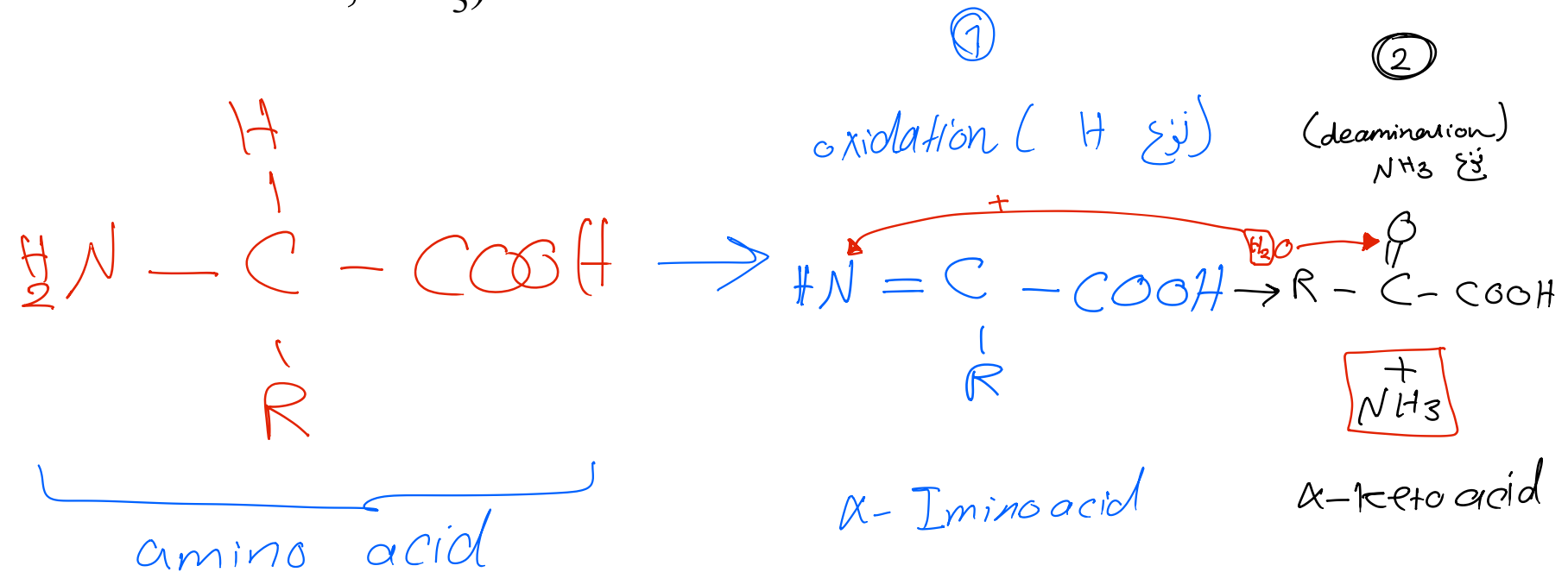
General catabolic pathways of amino acids

- Deamination:

1. Oxidative deamination.

Oxidative deamination

- ① By oxidative deamination reaction both oxidation (removal of hydrogen) and deamination (removal of ammonia, NH_3).



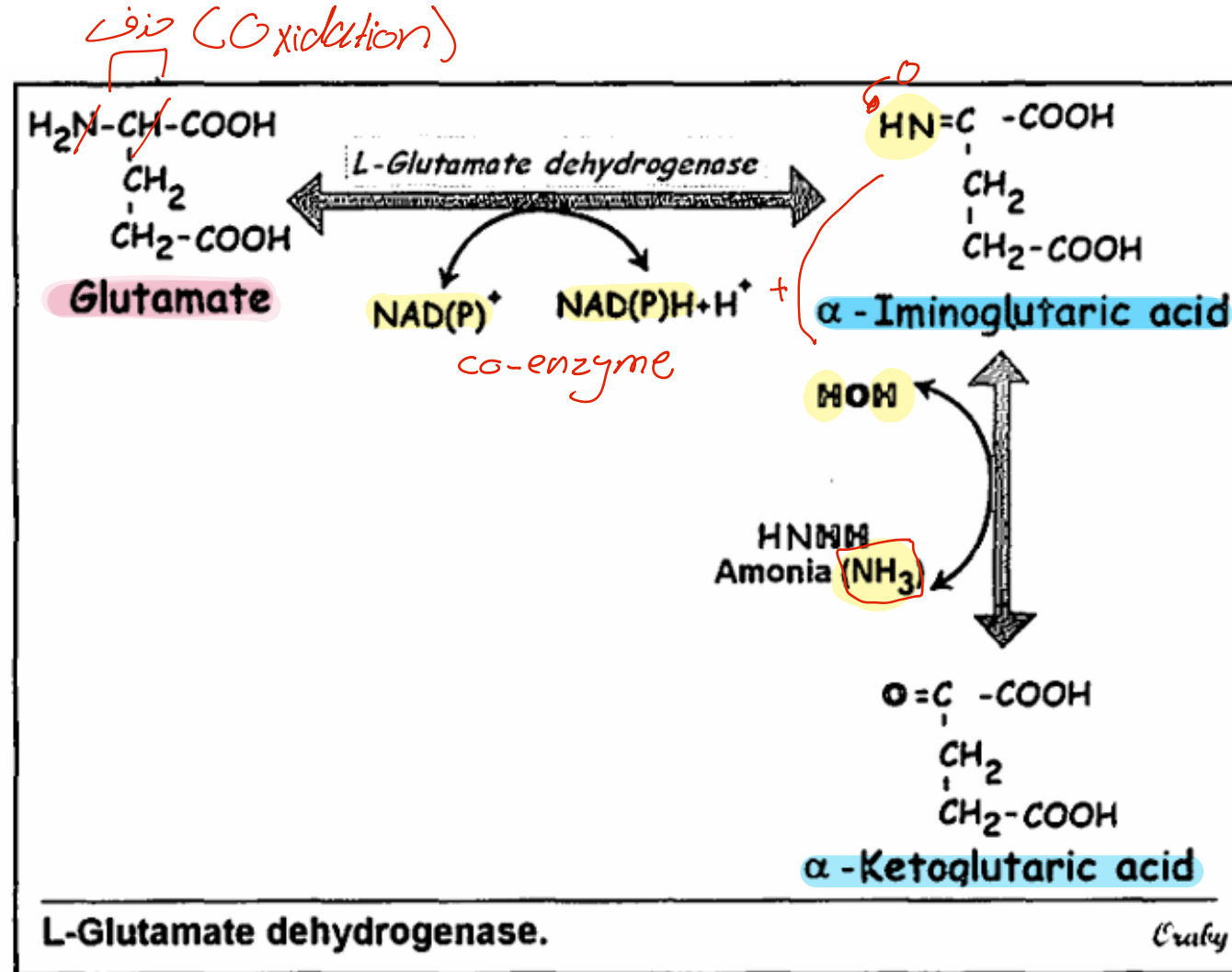
There are three main enzymes involved in oxidative deamination

1. L-glutamate dehydrogenase
2. L-amino acid oxidase
3. D-amino acid oxidase

Oxidative deamination by ^{bio} L-glutamate dehydrogenase

- It is highly active enzyme catalyzes the deamination of L-glutamate amino acid.
- This enzyme is present in both cytosol and mitochondria of most tissues.
- Its coenzyme is either NAD⁺ or NADP⁺.

Oxidative deamination by L-glutamate dehydrogenase

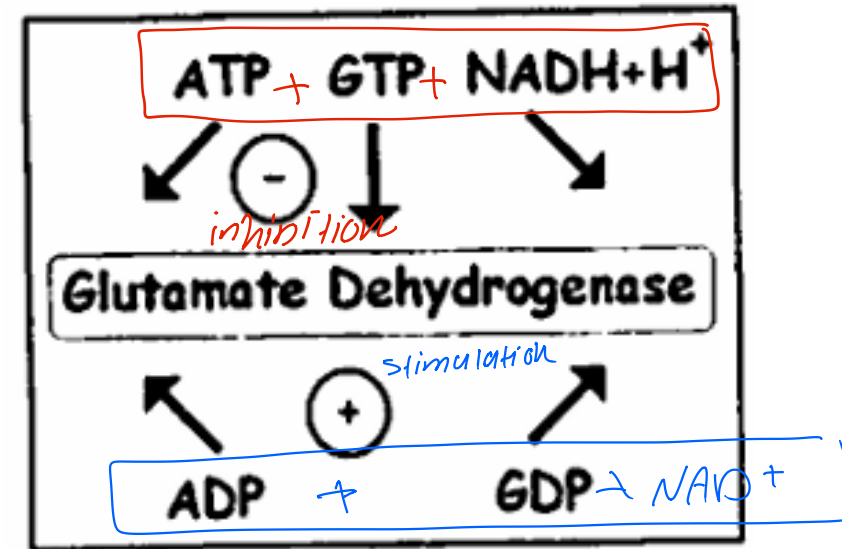


Regulation of L-glutamate dehydrogenase:

- ATP, GTP and $\text{NADH} + \text{H}^+$ allosterically inhibit L glutamate dehydrogenase.
- ADP, GDP stimulate it .
- Thus, its activity is increased when energy is required

نشاط الإنزيم لا يزيد لما الجسم يحتاج طاقة

أما لما يكون في حاجة زيادة جوف ATP يكون حار
إلى تنبيه



L-amino acid oxidase (LAAO):

سريع
C₂

- LAAO is a flavoprotein enzyme that can deaminate a wide range of L-amino acids.

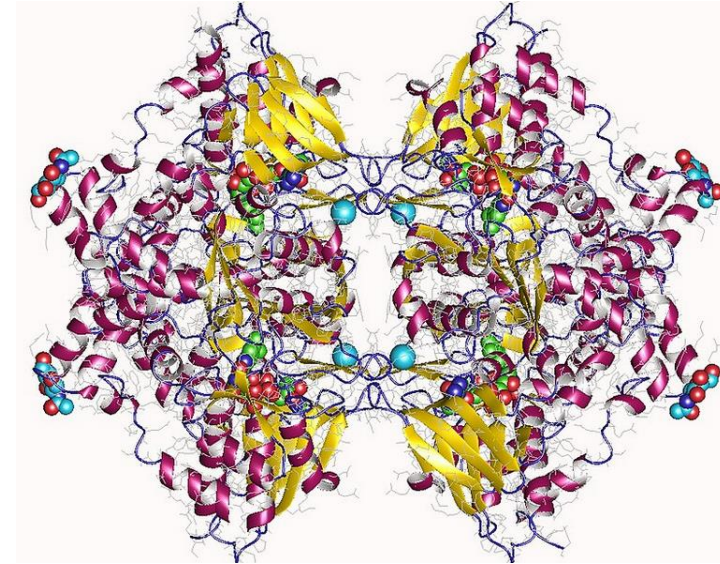
- Its coenzyme is FMN.

- The reaction produces alpha-keto acids, ammonia, and hydrogen peroxide (H₂O₂), as a side product. It is highly toxic to the cells.

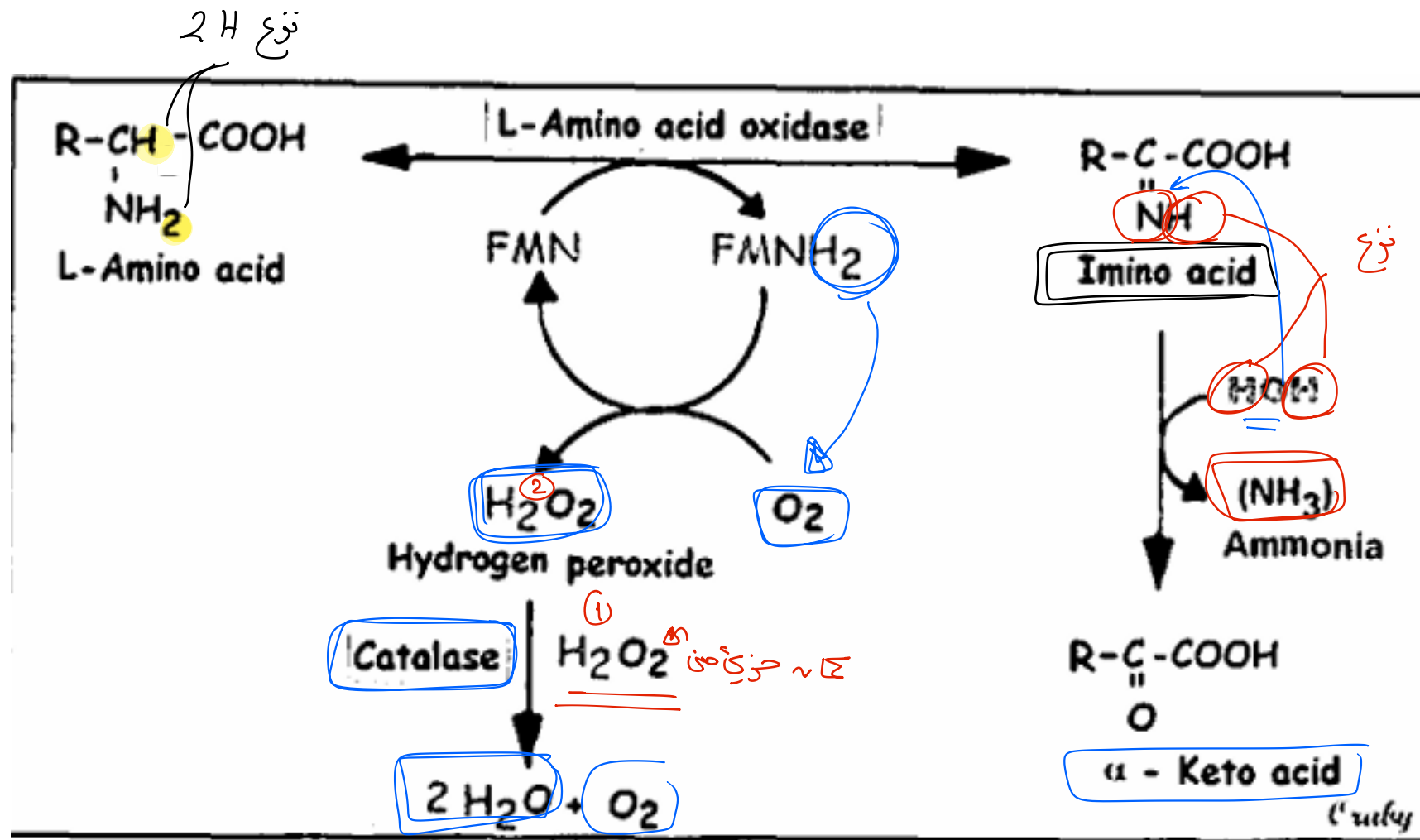
يحول ذلك إلى سلفيد هيدروجين

It is hydrolyzed rapidly by catalase into H₂O and O₂.

- LAAO is primarily found in the liver and kidney.



L-amino acid oxidase (LAAO): عنه نزع هيدروجين



Oxidative deamination by D-amino acid oxidase:

Diet *DI Golek Chap*

- D-amino acids are found in plants and in cell wall of microorganisms.
- They are not used in the synthesis of proteins inside the human body.
- D-amino acids present in diet are deaminated in the liver by D-amino acid oxidase.
- Its coenzyme is FAD .

General catabolic pathways of amino acids

- Deamination:

- 2. Non-oxidative deamination.

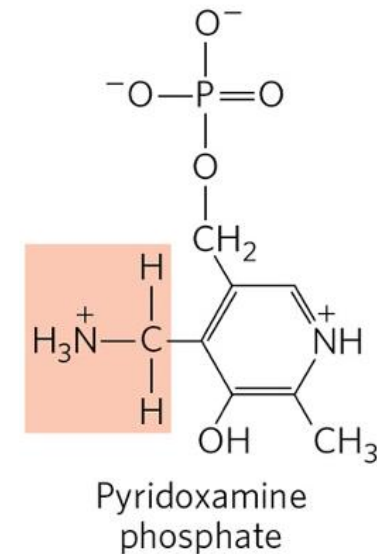
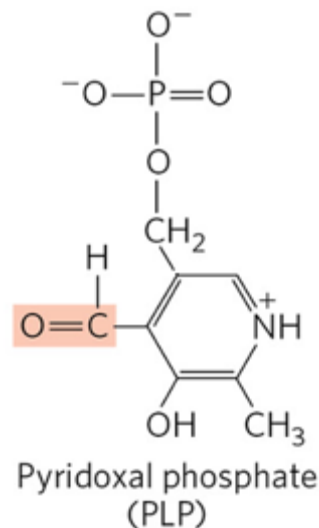
Non-oxidative deamination

هذه هي التفاعل H_2O

يتم على OH مع نزع جزيء الماء من خلاصة

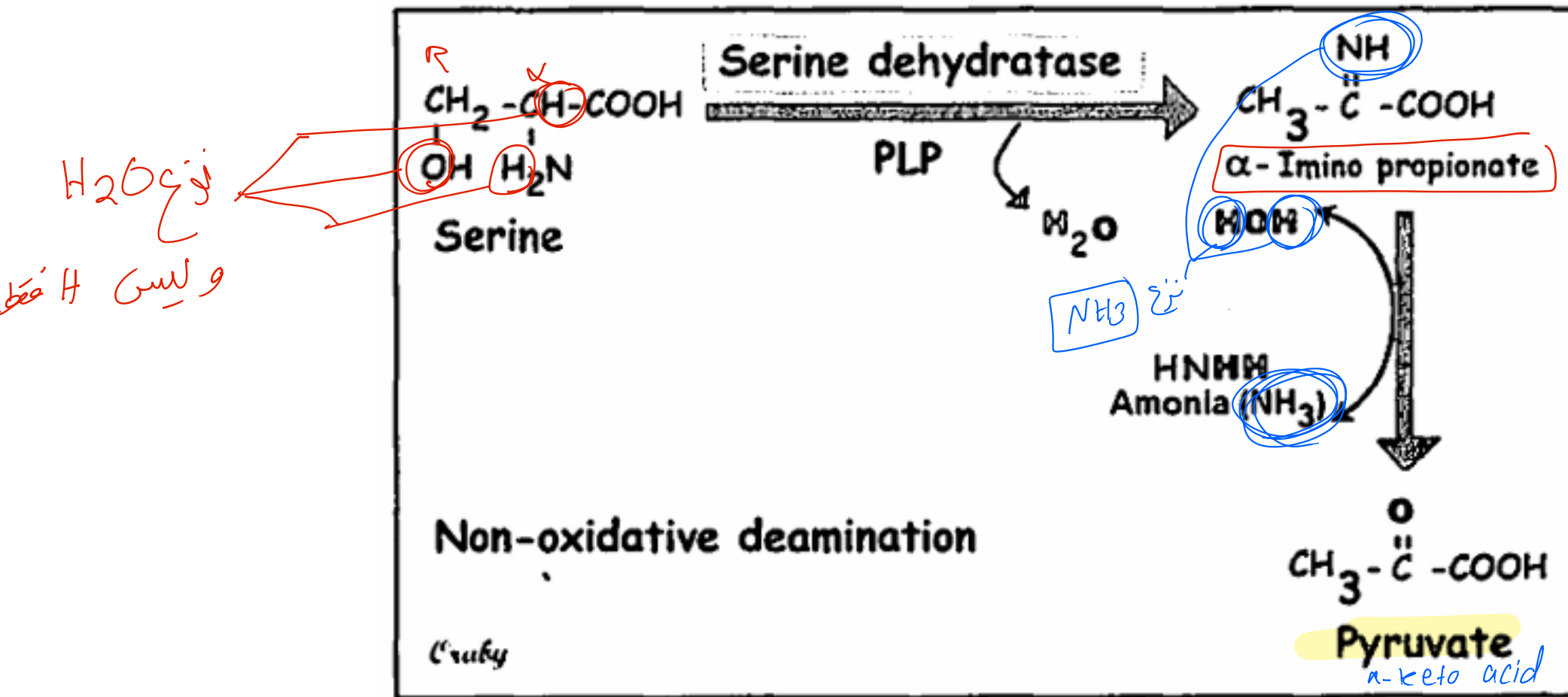
- This occurs for hydroxy amino acids e.g. serine, threonine, without removal of hydrogen (non-oxidative) $\longrightarrow$ Pyruvate.
- Its coenzyme is pyridoxal phosphate.

Vitamin B6



Pyridoxal phosphate (PLP) and its aminated form, pyridoxamine phosphate

Non-oxidative deamination



non-oxidation

General catabolic pathways of amino acids

- Deamination:

3. Hydrolytic deamination.

dicarboxylic acid (مجموعة الكربوكسيل خالوتين)

نزع H_2O

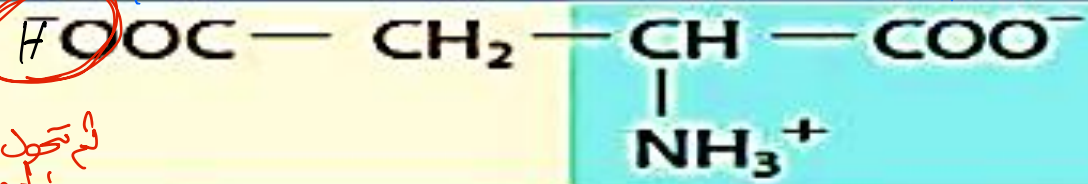
H

$HNH +$

H

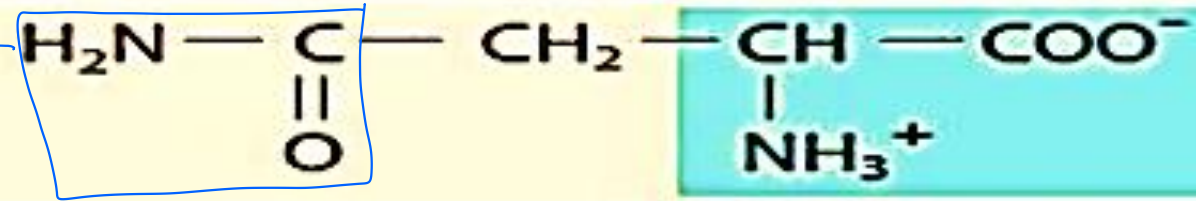
Aspartic acid

لم يتكون
الماء



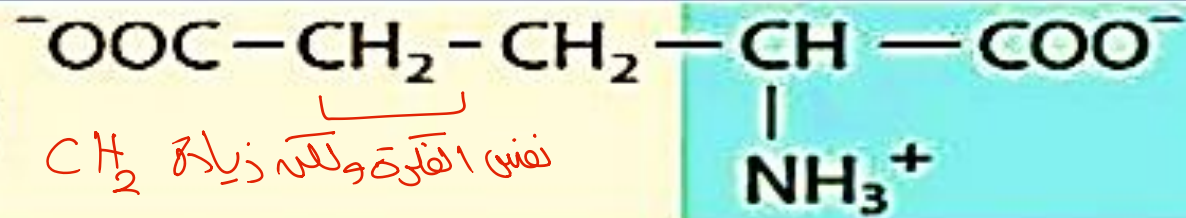
amide group

Asparagine

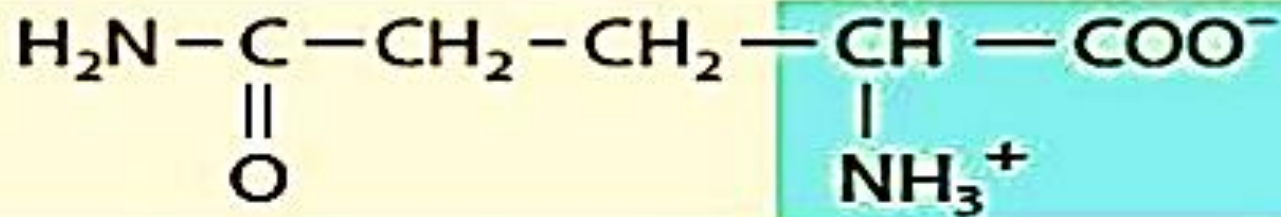


Glutamic acid

نفس الفكرة ولكن زيادة CH_2



Glutamine



يقول
ذكي

$$\text{Zn} + \text{H}_2\text{O} \rightarrow \text{ZnO} + \text{H}_2$$

- هو تجميع الأصول على وجه من وجه في كل من الأصول في الأصل

McLEYN

blood pH acidic
 H^+ increases
 NH_4^+ increases
 NH_4^+ increases
 NH_4^+ increases



Thanks



Medical Biochemistry

***Protein** Metabolism*

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

Al-Azhar University-Gaza



General catabolic pathways of amino acids

- Transamination

Transamination:

- Definition: It is the transfer of amino group from α -amino acid to α -keto acid to form a new α -amino acid and a new α -keto acid.

Mechanism:

- Enzymes called transaminases (or amino transferases) catalyze transamination reactions.
- PLP is the coenzyme for all transaminases. (Ly thr pr hy)
- All amino acids (except lysine, threonine, proline and hydroxyproline) may undergo transamination.
- All transamination reactions are reversible.
- All transaminases are present either in cytosol or in both cytosol and mitochondria of most tissues.
- Among all transaminases, 3 are present in most mammalian tissues and they are of clinical importance. These are: ALT, AST and glutamate transaminase .

آلانين ترانساميناز

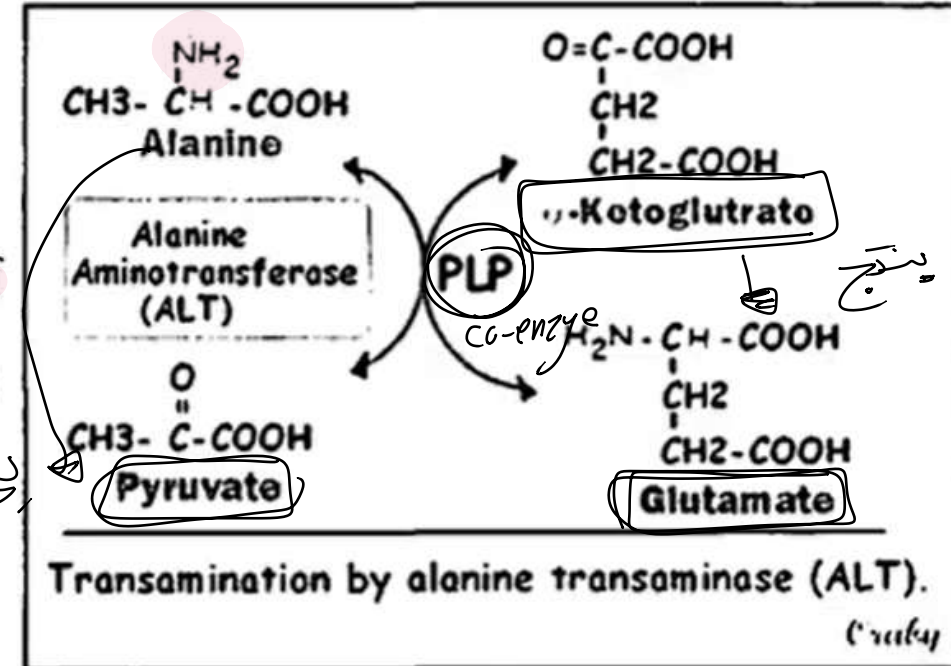
Alanine transaminase (ALT):

مع سكره
والتي
لا تتفكك
reversible

- ALT also called glutamate pyruvate transaminase

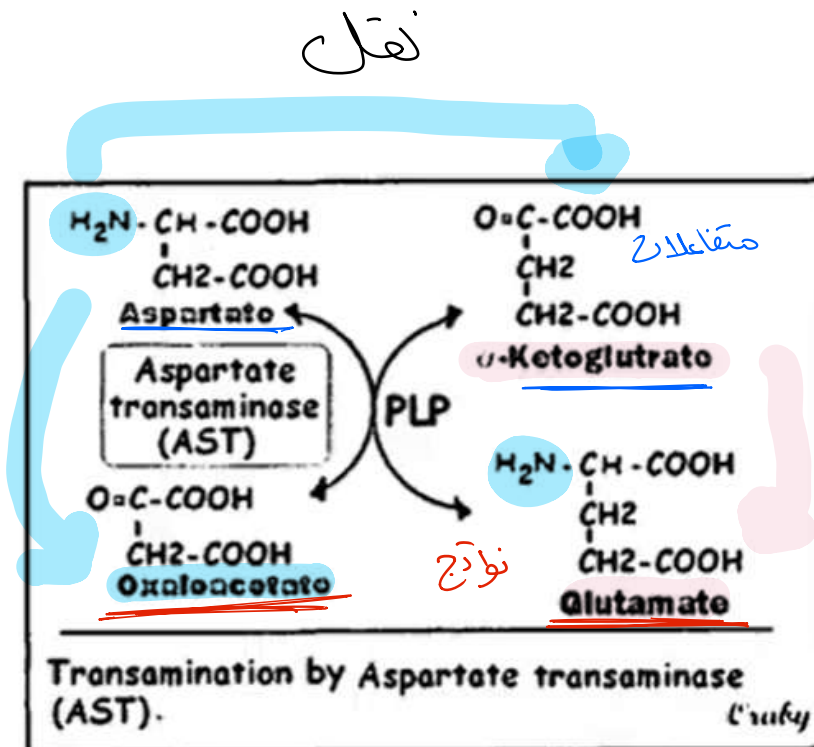
(GPT) أو (SGPT)
serum (جلوكاتون)

- ALT is present in the cytosol of the cells.
- ALT is an enzyme that catalyzes the transfer of amino group from alanine to α -ketoglutarate to form glutamate and pyruvate.
new α -keto acid new α -amino acid
- The reaction is reversible.



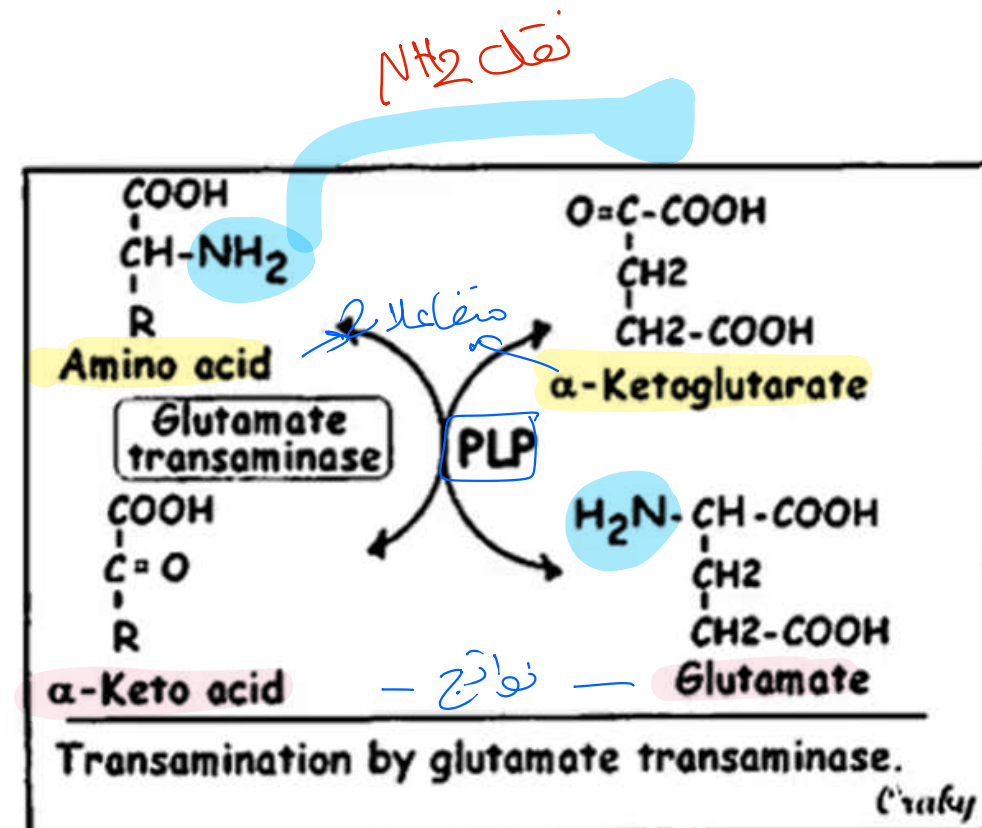
Aspartate transaminase (AST)

- AST is also called glutamate oxaloacetate transaminase (GOT). ^{في} (SGOT)
- AST is present in both cytosol and mitochondria of the cells
- AST is an enzyme that catalyzes the transfer of amino group from aspartate to α ketoglutarate to form glutamate and oxaloacetate.
- The reaction is reversible.



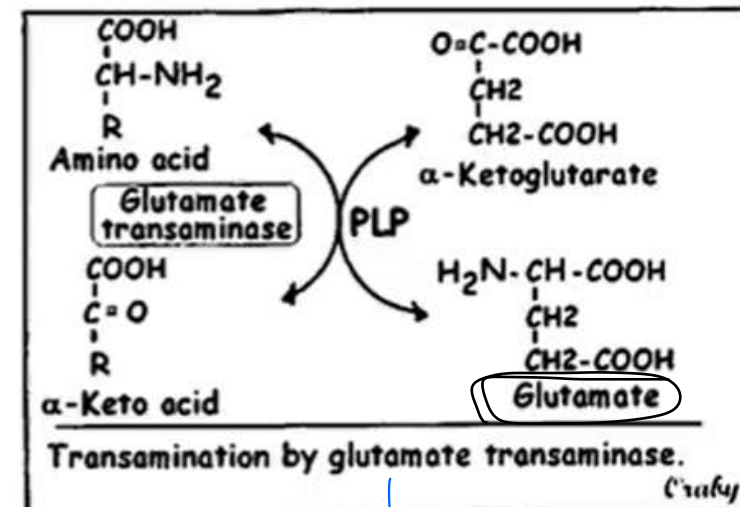
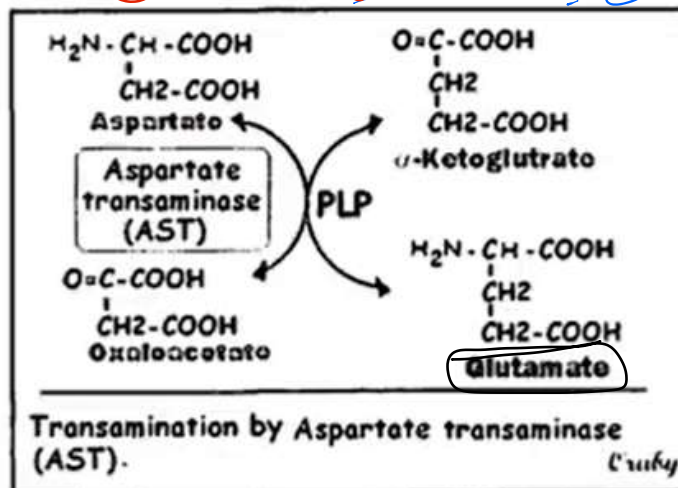
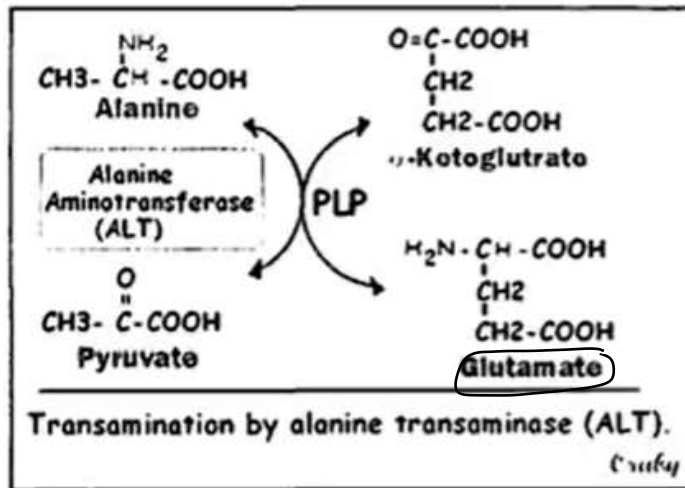
Glutamate transaminase:

- This enzyme catalyzes the transfer of amino group from any amino acid to α -ketoglutarate.



α -keto glutrate is the a.a donor

Glutamate is the a.a acceptor



General amino acid
exclude the exception

Functions of transamination:

- Transfer of amino group (NH_2) from most amino acids to α -ketoglutarate to form

glutamate. $\rightarrow$ deamination ده ازالة مجموعة الأمين

- Glutamate is then deaminated to give ammonia.

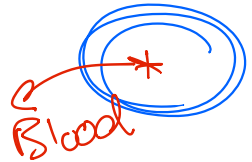
من خلال تفاعل
transamination تفاعل Glutamate

- Transamination is important for formation of non-essential amino acids

Glutamate + Alanine

$\underbrace{\hspace{10em}}$
reversible
reaction

Diagnostic importance of transaminases (ALT and AST):



يتم تصنيعها داخل الخلية فوجودها خارج
الخلية في الدم هذا يعني أن الخلية قد تضررت
وطغ بها

- Transaminases are normally intracellular enzymes.
 - The presence of elevated levels of transaminases in the blood indicates damage to cells producing these enzymes.
- Elevated levels of both ALT and AST indicate possible damage of liver cells with subsequent escape of hepatic enzymes into blood
- An elevated level of ^{Just} AST only suggests damage to heart muscle (myocardial infarction), skeletal muscle or kidney.