



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ ۝

CYTOLOGY

MID | Lecture 5

Mitochondria and peroxisomes

Written by : Dareen Alhababseh

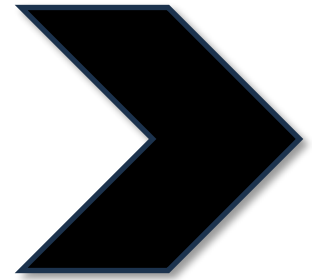
Hala Marei

Shahd Thamer

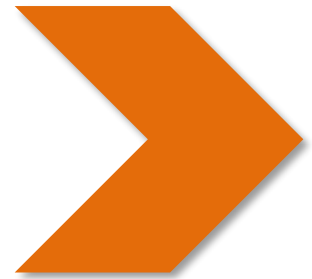
Reviewed by: Hala Marei & MST



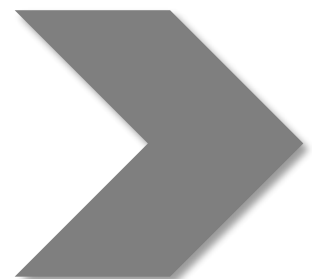
Color coding used in the modified:



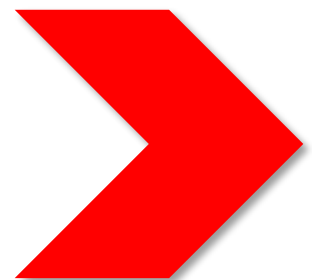
Black: the original slides



Orange: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

Lecture 3: Mitochondria and peroxisomes)



Prof. Mamoun Ahram
School of Medicine

Second year, First semester, 2025-2026

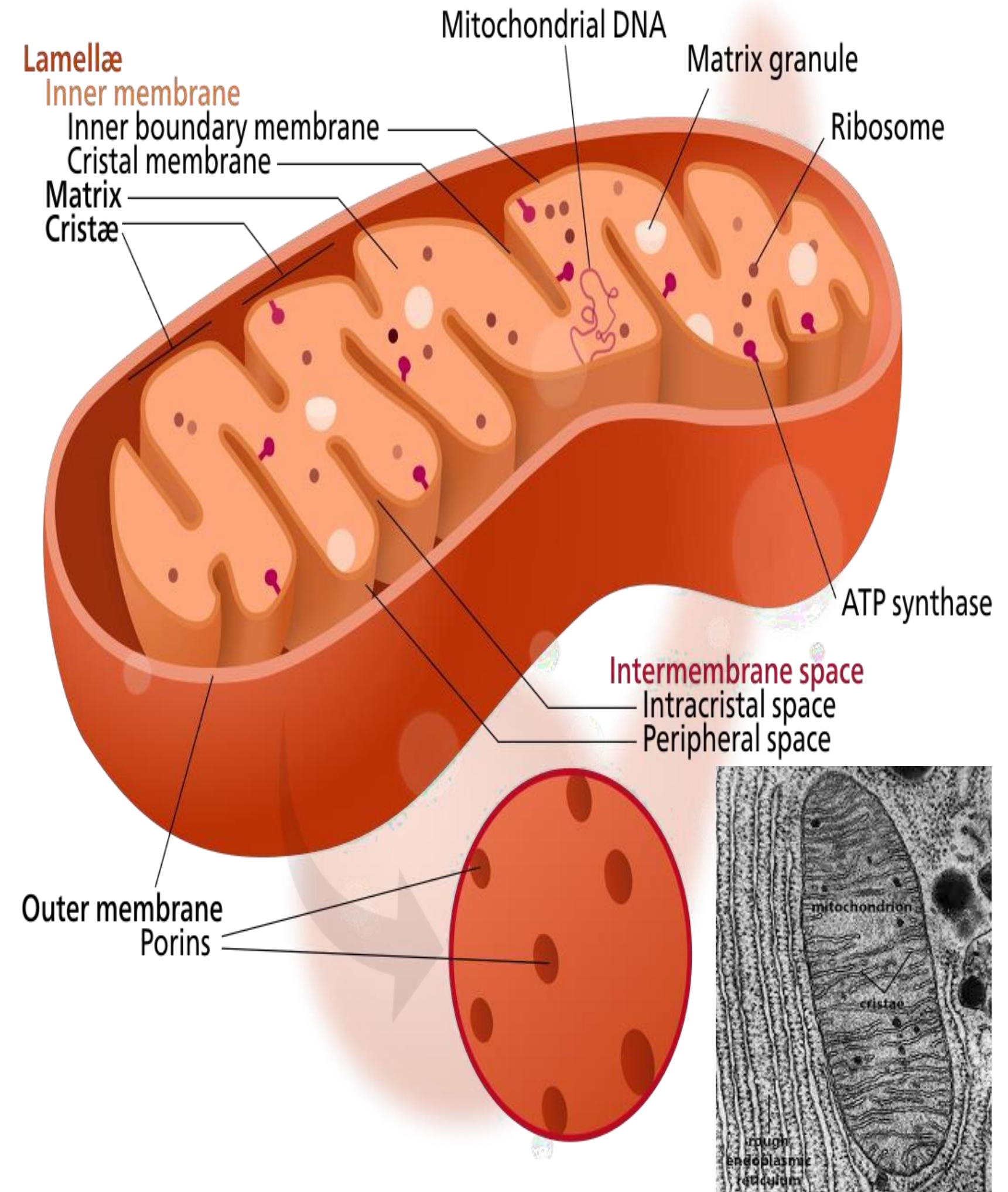
The mitochondrion is similar to bacteria, and scientists think that mitochondria were originally bacteria that fused with archaeal cells.

Mitochondria are found in eukaryotic cells, and eukaryotic cells and archaeal cells are different and have different proteins.

The inner membrane is convoluted because it contains the respiratory system, which consists of four complexes that make up the electron transport chain. These electrons move through the electron transport chain, and the energy released is used to pump protons into the intermembrane space.

The protons then accumulate in the intermembrane space, and they all move back through a channel called ATP synthase. As the protons pass through ATP synthase, ATP is generated inside the mitochondrial matrix.

So, we have an outer membrane, an inner membrane, and an intermembrane space between them. Inside the inner membrane, we have the mitochondrial matrix, which contains metabolic enzymes that are involved in metabolism. The Krebs cycle also occurs in the mitochondrial matrix and produces molecules that contribute to ATP generation.



What are the mitochondria?

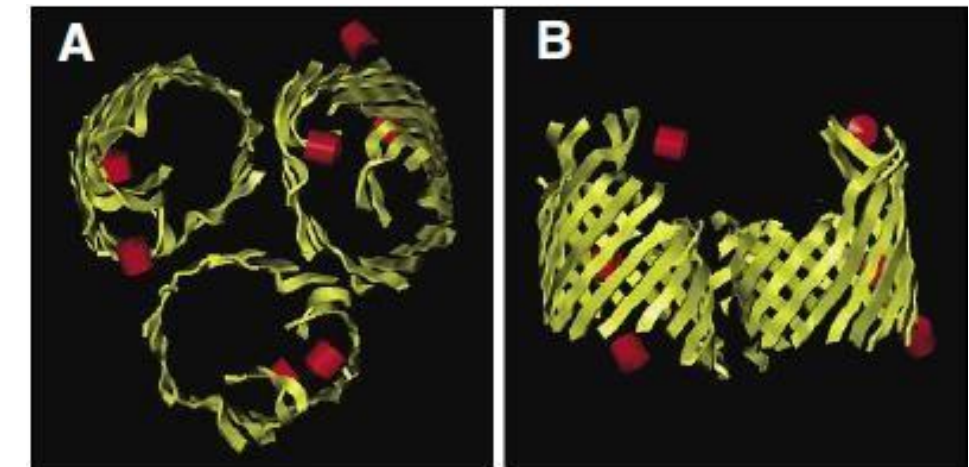
- Mitochondria are specialized organelles that play a critical role in the generation of metabolic energy in eukaryotic cells
 - Generation of ATP from the breakdown of carbohydrates and fatty acids
- They contain their own DNA (**circular**) (typically 2-10 copies), which encodes 37 genes (tRNAs, rRNAs, and 13 mitochondrial proteins).
 - transfer RNA Carries amino acids to the ribosome for protein synthesis.
 - Forms the ribosomes, which are responsible for protein synthesis.
 - These proteins that makes protein complexes
 - But most mitochondrial proteins (~1500) are encoded by the nuclear genome.
 - This means that only 13 of them are encoded by their own mitochondrial DNA, while the majority are encoded by nuclear DNA.
- Most mitochondrial proteins are translated on free cytosolic ribosomes and imported into the organelle.
- They are thought to have evolved from bacteria via endosymbiosis.

Structure

- Outer membrane **Porous**
 - permeable to small molecules (~1000 Da) because of porins (channel proteins)
- Inner membrane **Selective**
 - contains a high percentage (>70%) of proteins (30% lipids)
 - Forms folds (cristae) to increase surface area so that it can accommodate the largest possible number of proteins.
 - Function; oxidative phosphorylation, ATP generation, transport of metabolites
 - impermeable to most ions and small molecules
- Intermembrane space
- Matrix
- contains the mitochondrial genetic system and the enzymes responsible for the Krebs cycle

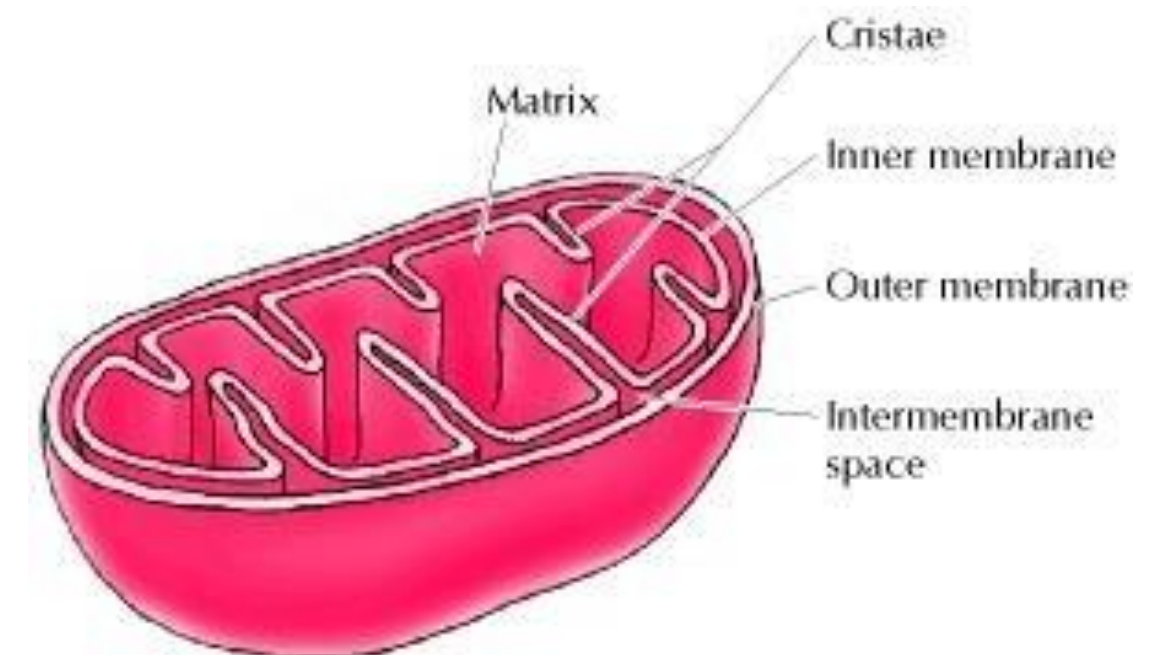
Here, we have three openings called **porins**, and there is no strict control over the passage of small molecules through them.

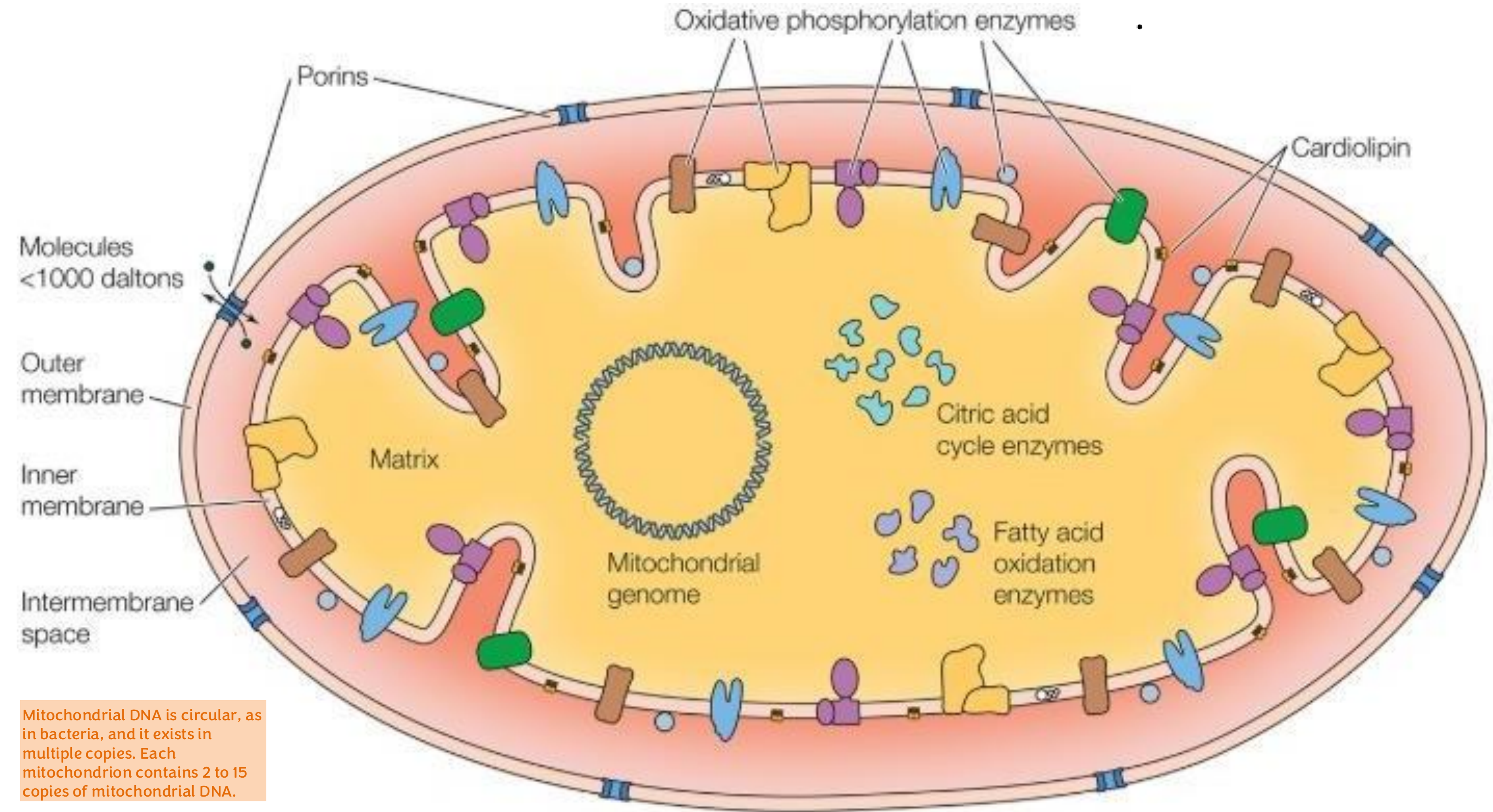
The structure here consists of **β -strands**, similar to those found in bacteria.



Top view

Side view





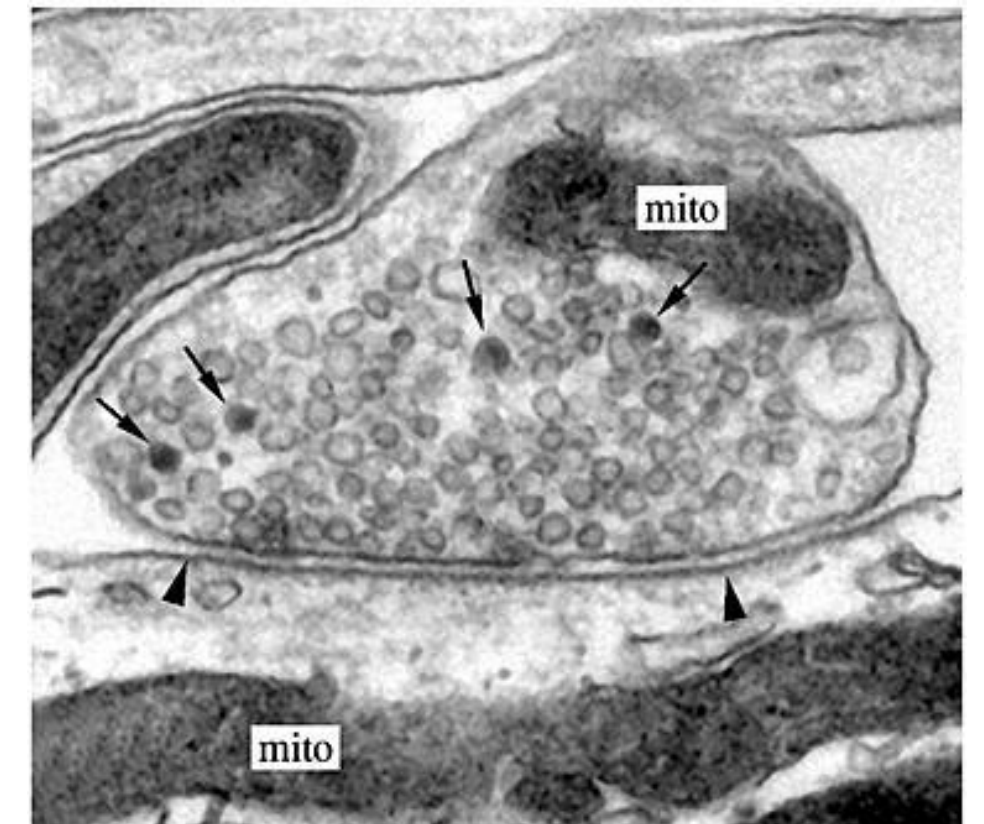
Properties and features

Because mitochondria are located in cells that generate energy, the more energy a muscle cell needs, the more mitochondria it tends to have.

How does the number of mitochondria increase?

It increases through mitochondrial fusion and fission.

- They are located in cells requiring high-energy use such as synapses.
- They are dynamic (fusion versus fission or division)



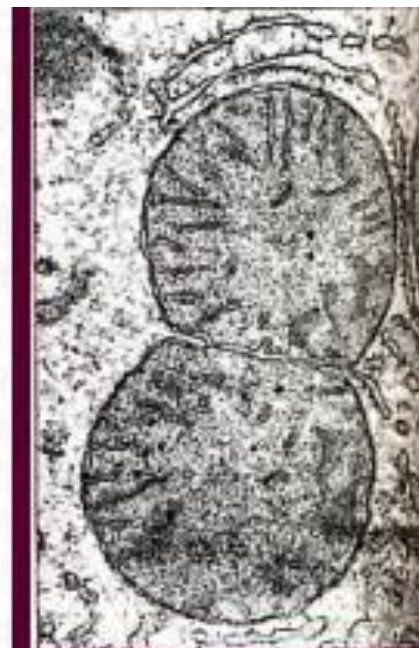
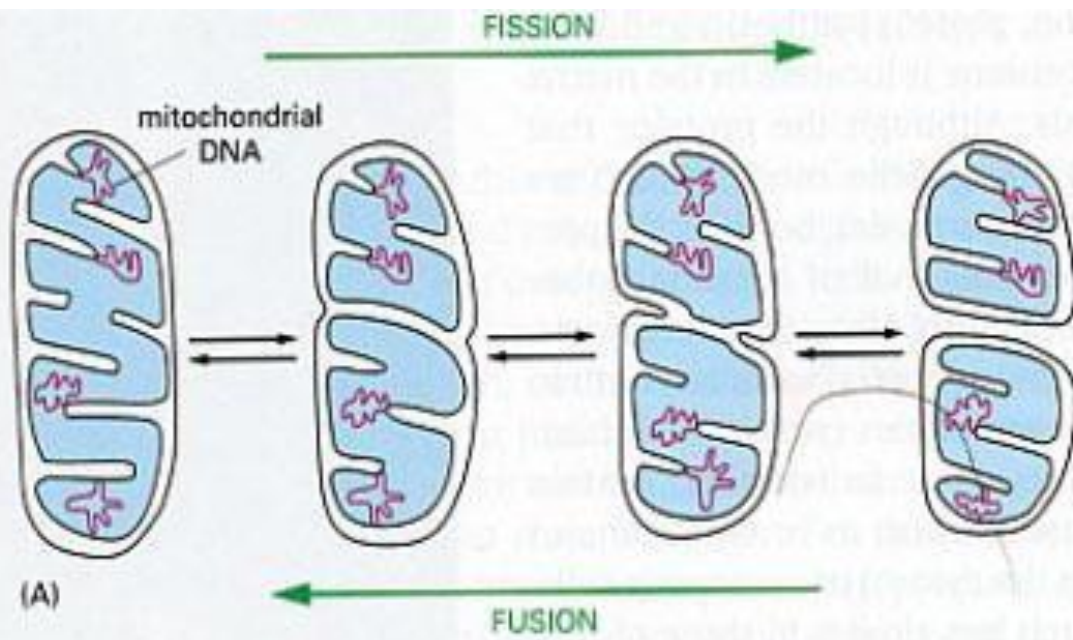
- Advantages**
- Exchange genetic material *Example in the next slide*
 - Transfer to daughter cells
 - Regulate autophagy
 - Cell survival and apoptosis *(Programmed cell death)*
 - Energy demand

When we have two mitochondria, they can fuse together to form one larger mitochondrion.

When we have one mitochondrion, it divides into two mitochondria.

- Increase in mitochondrial oxidative capacity *& Production of radicals and ATP*
- Repair of reversibly damaged mitochondria
- Limitation of mtDNA mutations during aging

- Increase in resistance to oxidative stress
- Segregation of damaged mitochondria
- Mitophagy *Eating mitochondria*



- Exchange genetic material

Example : I have one mitochondrion that contains 10 copies of mitochondrial DNA. When it undergoes **fission**, it divides into two mitochondria: one may contain 10 copies of mitochondrial DNA, and the other may contain 4 copies.

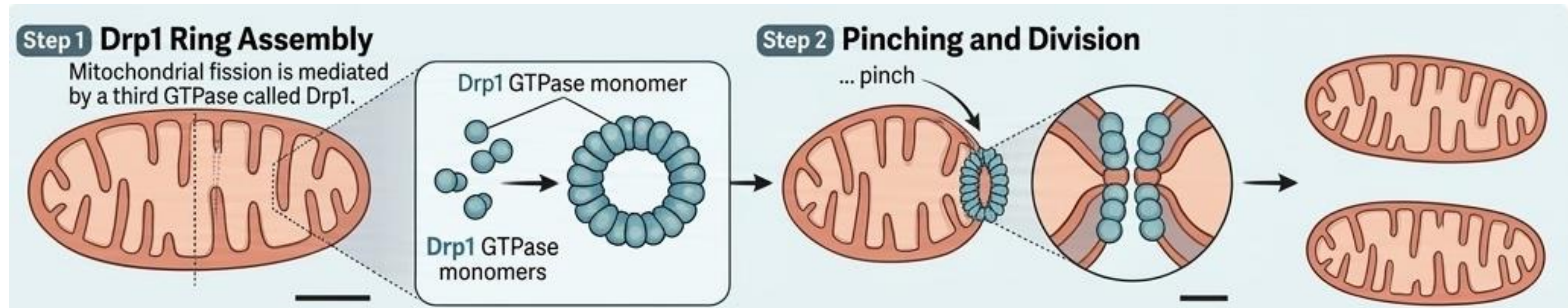
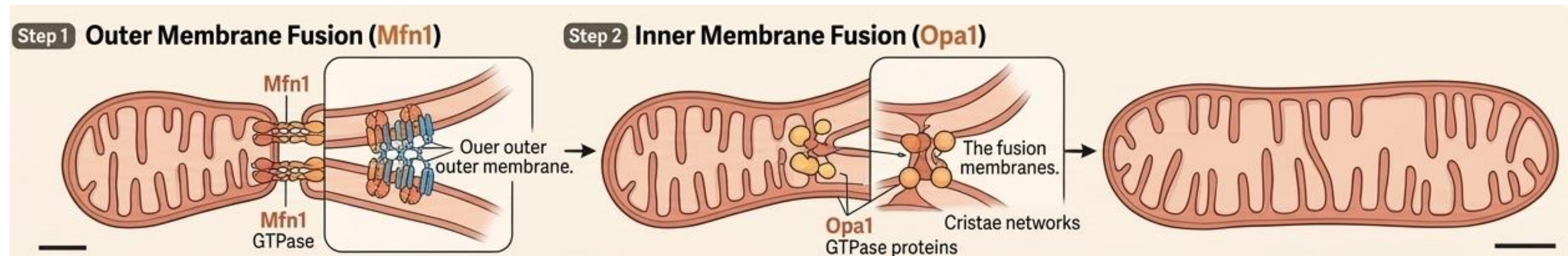
Another example: I have two mitochondria, one containing 4 copies and the other containing 6 copies of mitochondrial DNA. They undergo **fusion** and form one mitochondrion containing 10 copies. Then, when it undergoes fission, it may divide into two mitochondria, each containing 5 copies. This can facilitate the sharing of genetic material between mitochondria.

Note: If we have damaged DNA, the mitochondrial of the DNA cannot be repaired. It can only be repaired by fusion and fission. So one of the death reasons is the accumulation of defected chromosomes in the mitochondria so it no longer you can make ATP.



The molecular mechanisms of fusion/fission

- Mitochondrial fusion and fission are driven by **GTPase proteins**.
 - **Mfn1** is responsible for the fusion of the outer membrane, whereas **Opa1** then mediates the fusion of the inner membranes.
 - Mitochondrial fission is mediated by a third **GTPase** called **Drp1**, which assembles into a ring structure around a mitochondrion, resulting in its pinching and fission. **Drp1 is important for fission**

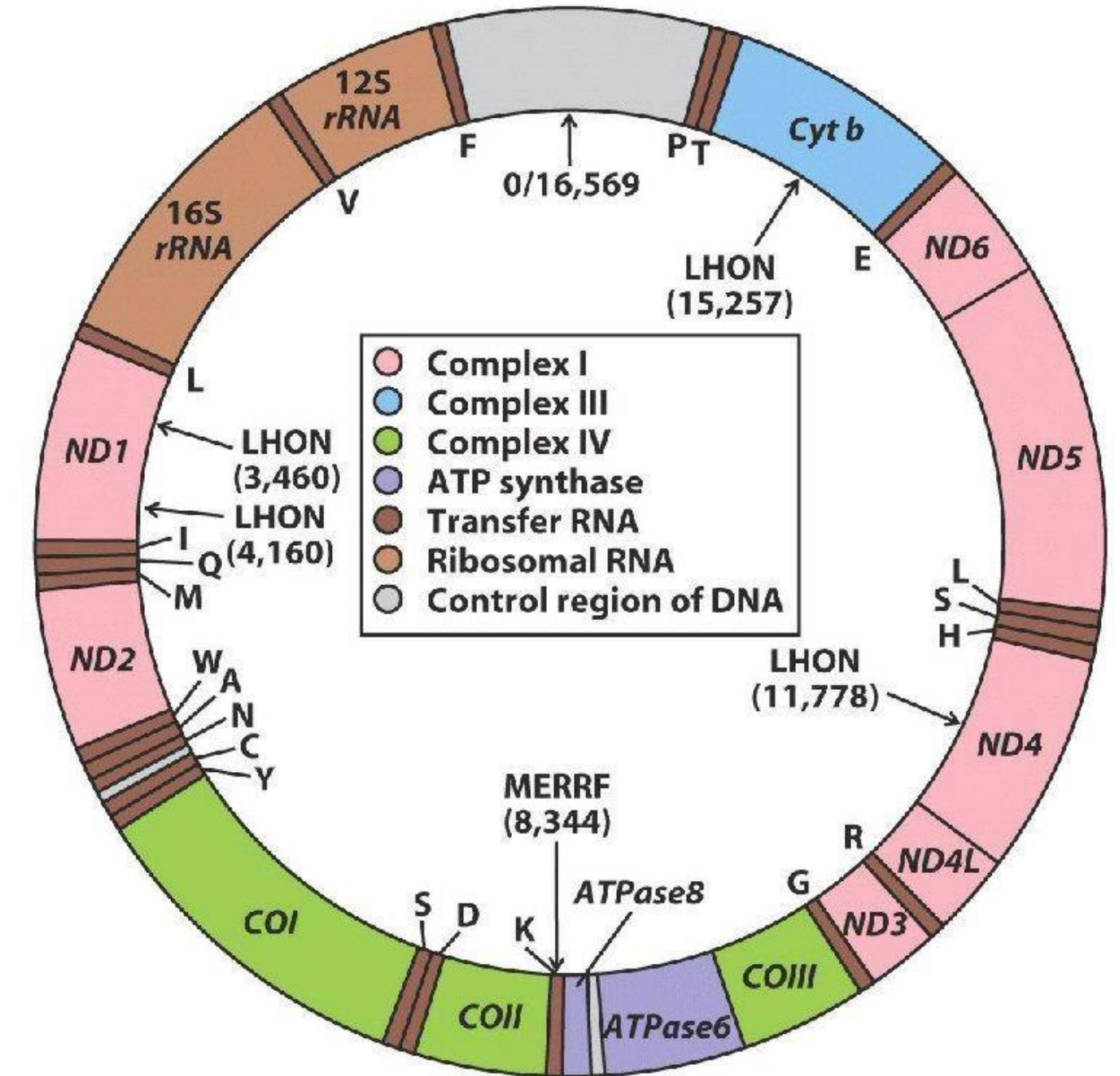


The Genetic System of Mitochondria

- Mitochondrial DNA (~16 Kb) is circular and exists in multiple copies per organelle.
- It encodes 13 proteins involved in electron transport and oxidative phosphorylation, rRNAs, and tRNAs.
- The oocytes are the main source of the mitochondria, meaning that mutations in the mitochondrial DNA are inherited from the **mother**.

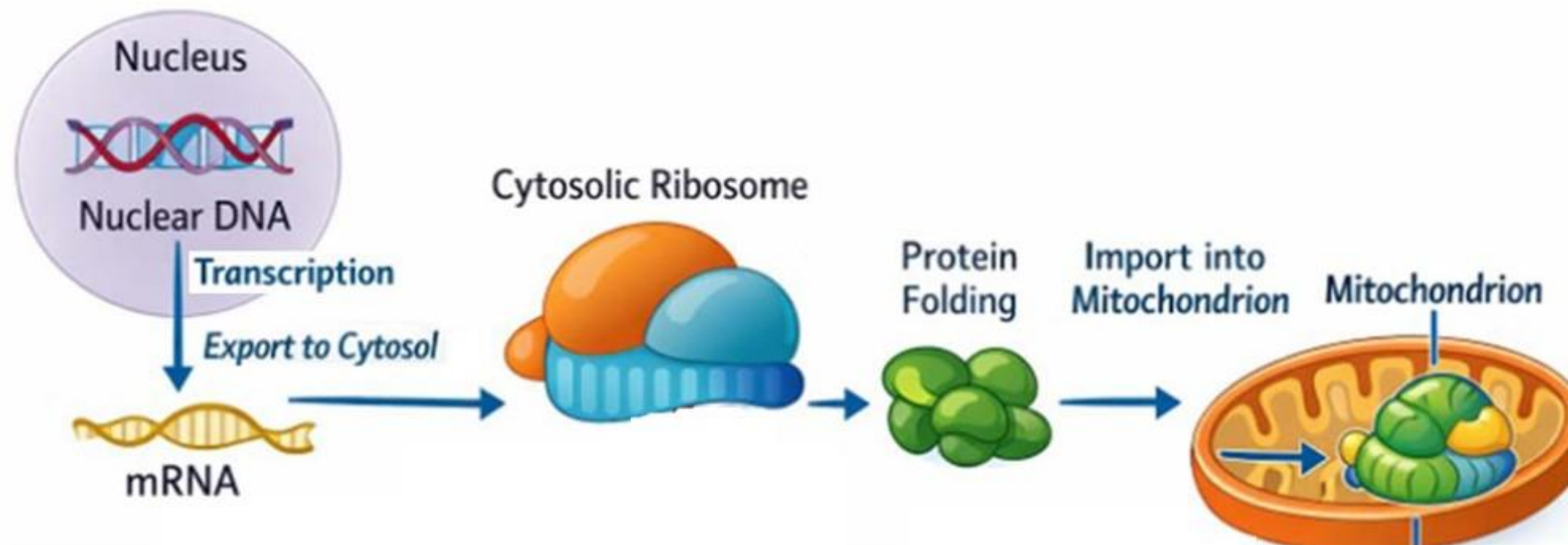
One of the ways to study the origin of the human is to study the mitochondria because it's way simpler than studying the two genomes from the parents.

Mitochondrial genome



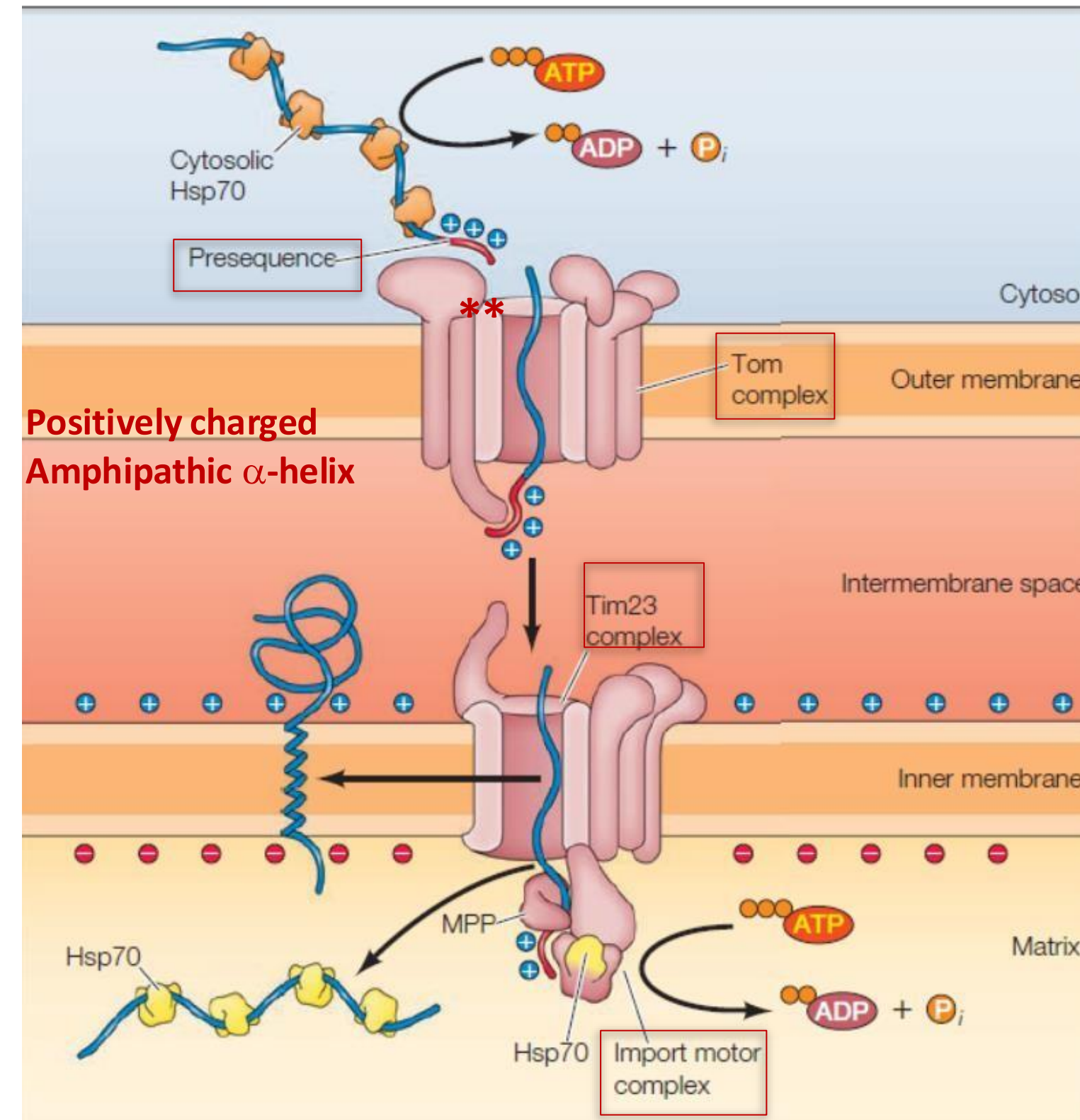
Mitochondrial proteins

- The nuclear genome encodes for most mitochondrial proteins including those required for DNA replication, transcription, translation, oxidative phosphorylation, and enzymes for mitochondrial metabolism.
- The proteins encoded by these genes (~99% of mitochondrial proteins **comes from the nuclear DNA, and the rest come from the mitochondrial DNA, about 13 proteins**) are synthesized on free cytosolic ribosomes and imported into the mitochondria as completed polypeptide chains.

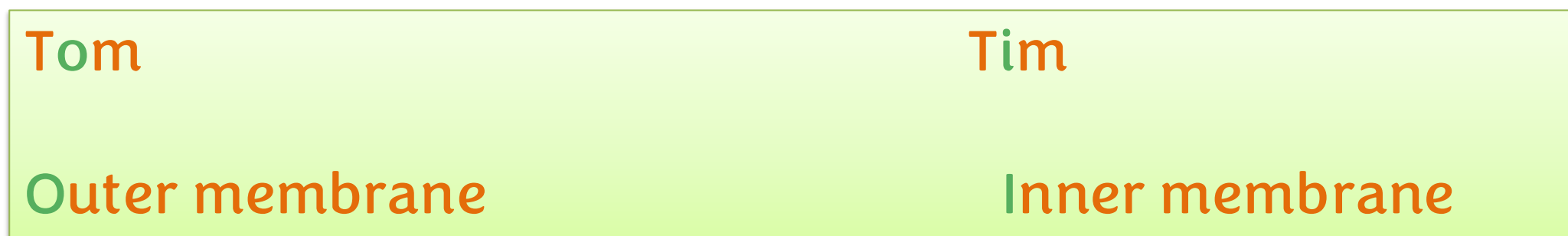


Protein Import and Mitochondrial Assembly

- Proteins are targeted to the Tom complex in the mitochondrial outer membrane by N-terminal **presequences**.
- The protein passes through a channel protein (translocase) called the **Tom complex** on the outer membrane followed by passing through another channel (translocase) called the **Tim complex** in the inner membrane.
- **Tom & Tim enters the polypeptide in the mitochondria**
- The presequence is then removed and
- protein folding is completed.
- **Some proteins with transmembrane domains exit the inner membrane channel laterally into the inner membrane.**

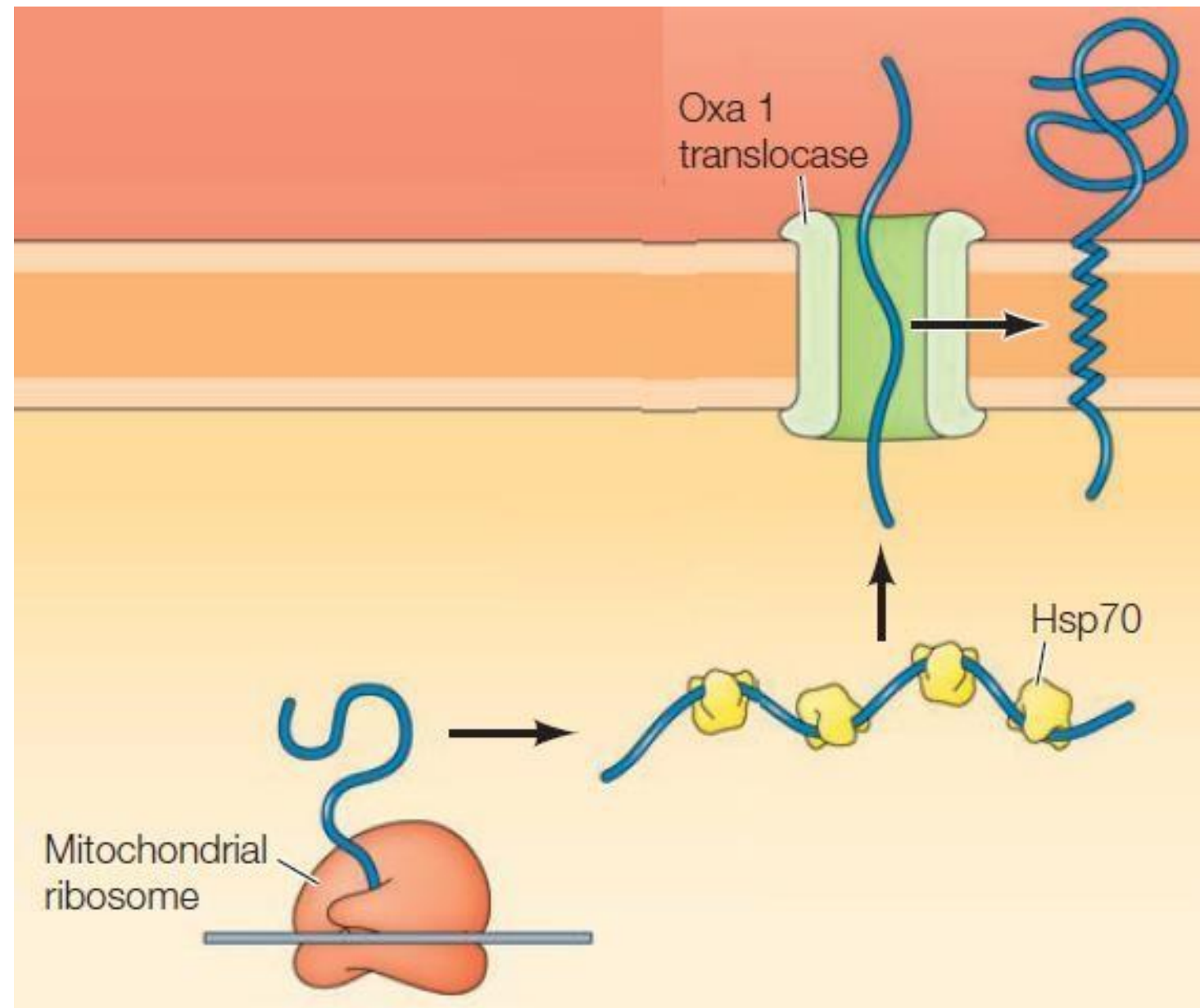


- Presequence is recognised by a group of proteins called heat shock proteins HSP which carry the body's proteins tightly into the mitochondria.
- Inside the mitochondrial matrix, we will have protein folding. The proteins who want to go to the inner membrane as they are going through Tim they are pushed aside so it becomes a part of the membrane.



Targeting of inner membrane proteins

- Some inner membrane proteins encoded by the mitochondrial genome are inserted via **Oxa translocase**.

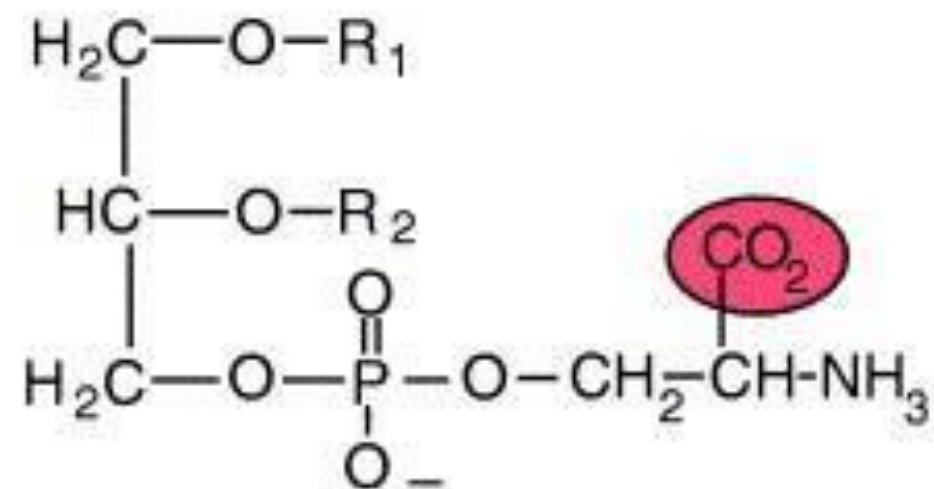


They are synthesized in the mitochondrial matrix; then the HSP carries them to the inner membrane to enter a channel called Oxa translocase (it recognizes that this protein should enter the inner membrane, so it pushes it to the inner membrane, just like the Tem working method)

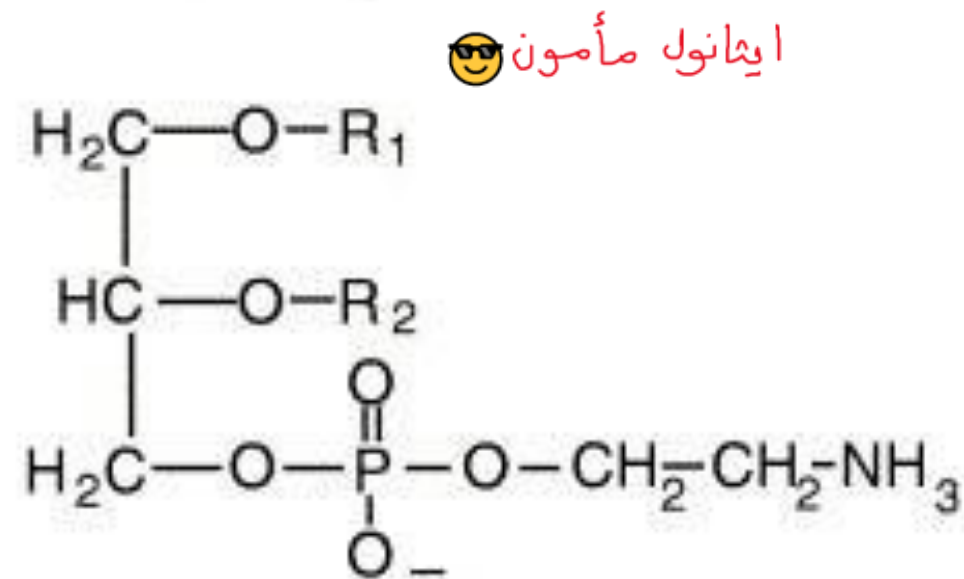
Mitochondrial phospholipids Phosphatidyl...

- Phosphatidylcholine and phosphatidylethanolamine (glycerophospholipids) are synthesized in the ER and carried to mitochondria by proteins.
- Phosphatidylserine can then be synthesized from phosphatidylethanolamine in the mitochondria.
- Glycerophospholipids = glycerol backbone + 2 fatty acid in C1 & C2 + C3 has phosphate (this is phosphatidate which is the precursor for all Glycerophospholipids which then we add to the P on C3 different molecules)

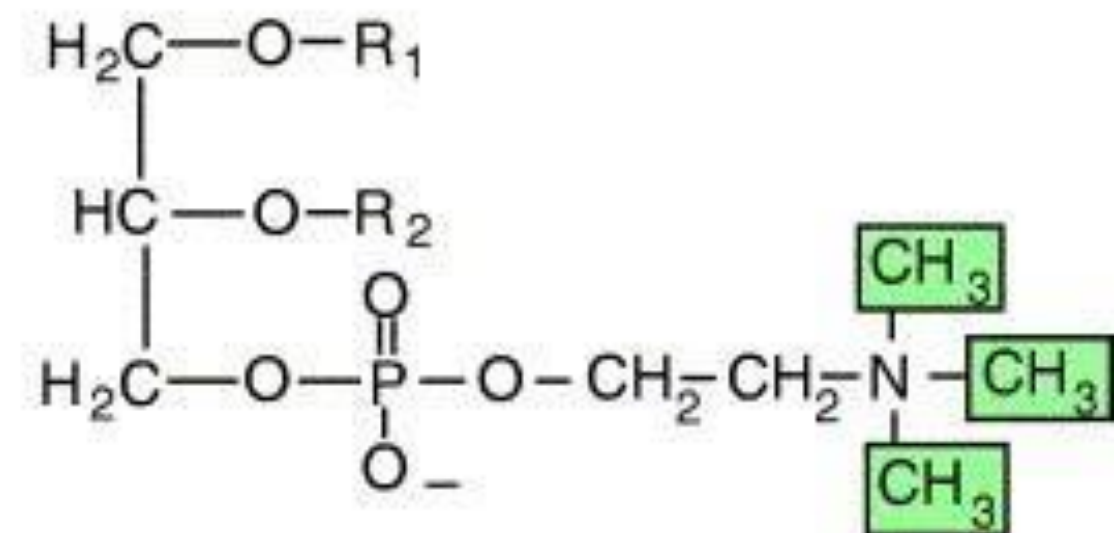
Phosphatidylserine



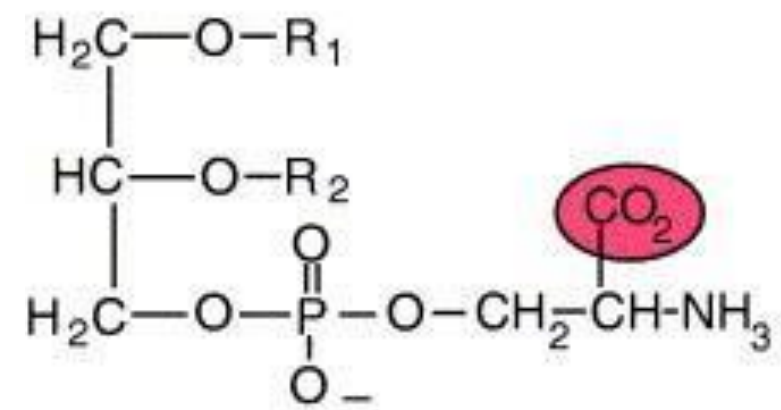
Phosphatidylethanolamine



Phosphatidylcholine

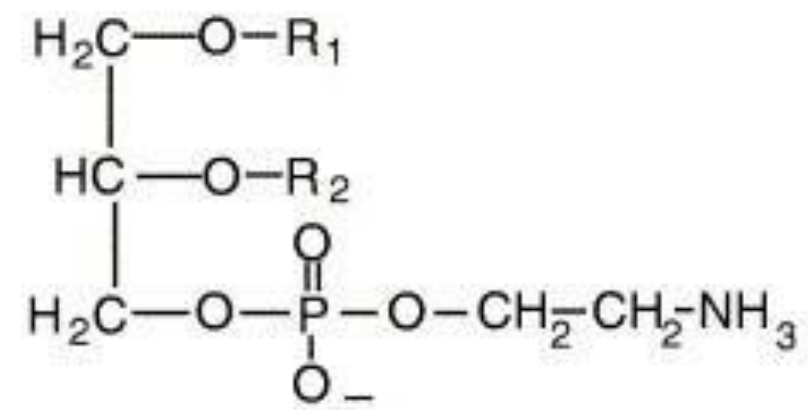


Phosphatidylserine



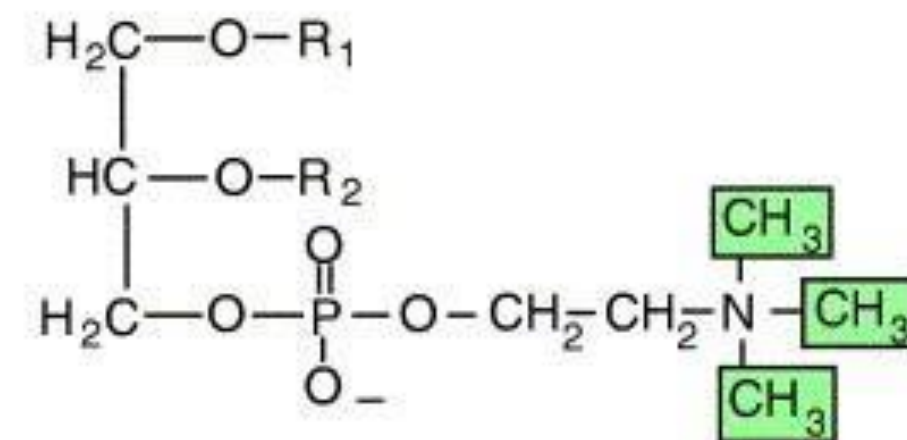
We put fatty acid at the first and second OH in the third one we put phosphate group that's why we called it phosphoglycerolipid then we put a head group these group could be ethanol, amine or choline or serine or inositol

Phosphatidylethanolamine



It consists of two carbon and amino group, that's why two carbon with amino group

Phosphatidylcholine



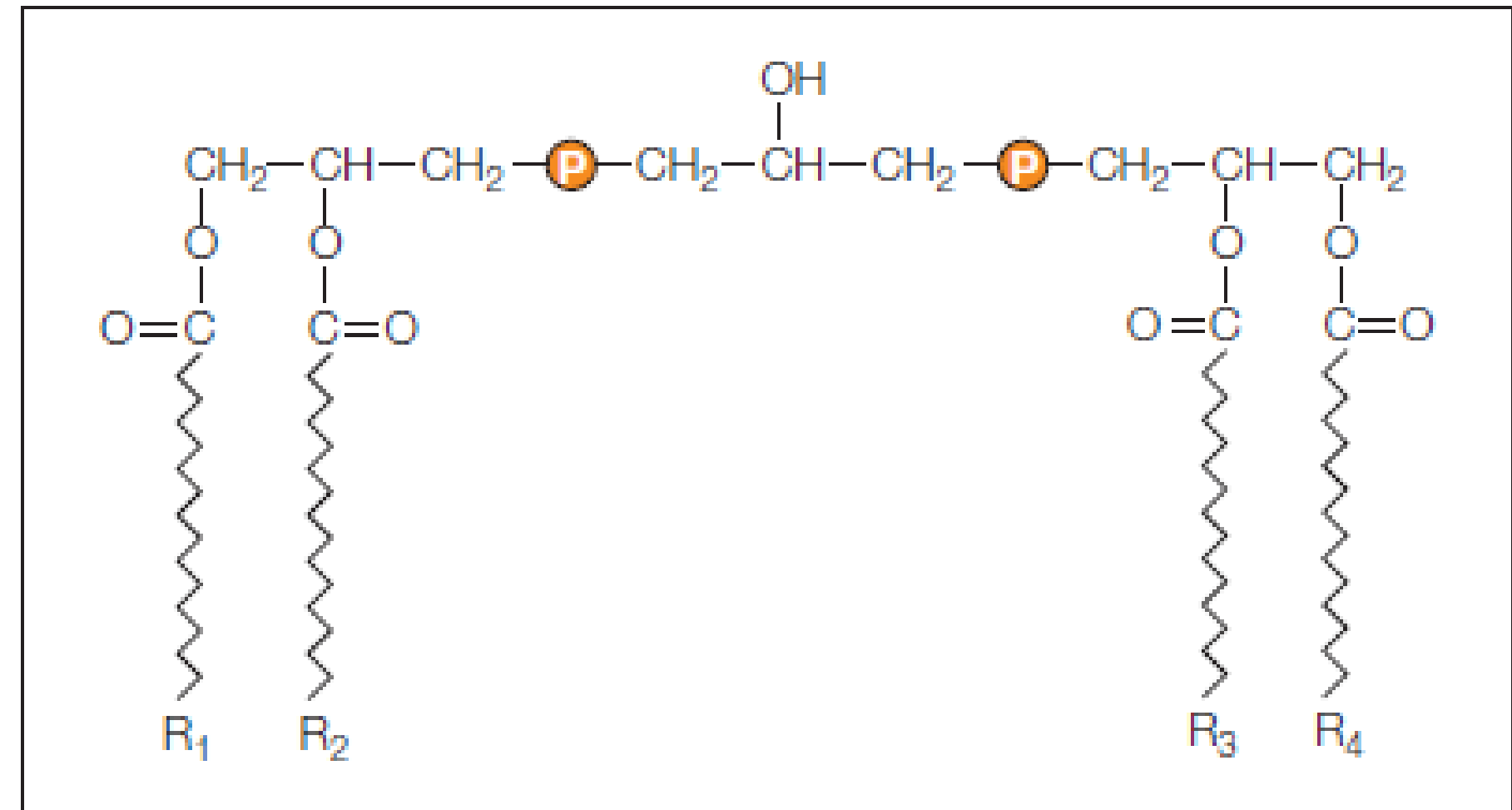
It has two carbon with nitrogen (amine group) and we have three methyl groups attached with it

Mitochondrial phospholipids Cardiolipin

- The unusual phospholipid, cardiolipin, which contains **four** fatty acid chains, is also synthesized in the mitochondria.
- This molecule improves the efficiency of oxidative phosphorylation by **restricting proton flow across the membrane.**
- It is also involved in the mitochondrial dynamics of fusion and fission.

Exists extensively in the cardiac tissue, which is a large molecule.
It also exists in the CNS

In the mitochondrial matrix there is a production for NADH & FADH₂ so complex one takes e from NADH & complex 2 takes e from FADH₂, then post two complexes gives the electrons to complex 3 which gives it to 4. Then e get bumped out from the matrix to the intermembranous space creating gradient in protons which then enter by protein ATP synthase which is very fast to create ATP





Mitochondrial diseases

NOTES:

1. Mitochondrial DNA can NOT be repaired.
2. The most affected tissues are cardiac tissue and CNS
3. Mitochondrial diseases are maternally inherited, somehow males are more affected .
4. The mother could be healthy, but the ovum has defective mitochondria



General information

- If the mitochondrial genomes carry a deleterious mutation, the embryo/fetus would generally not survive.
- Some mothers carry a mixed population of both mutant and normal mitochondrial genomes.
- Daughters and sons can inherit this mixture of normal and mutant mitochondrial DNAs and look healthy.
- In cases of mitochondrial defects, muscle and nervous tissues are most at risk, because of their need for particularly large amounts of ATP



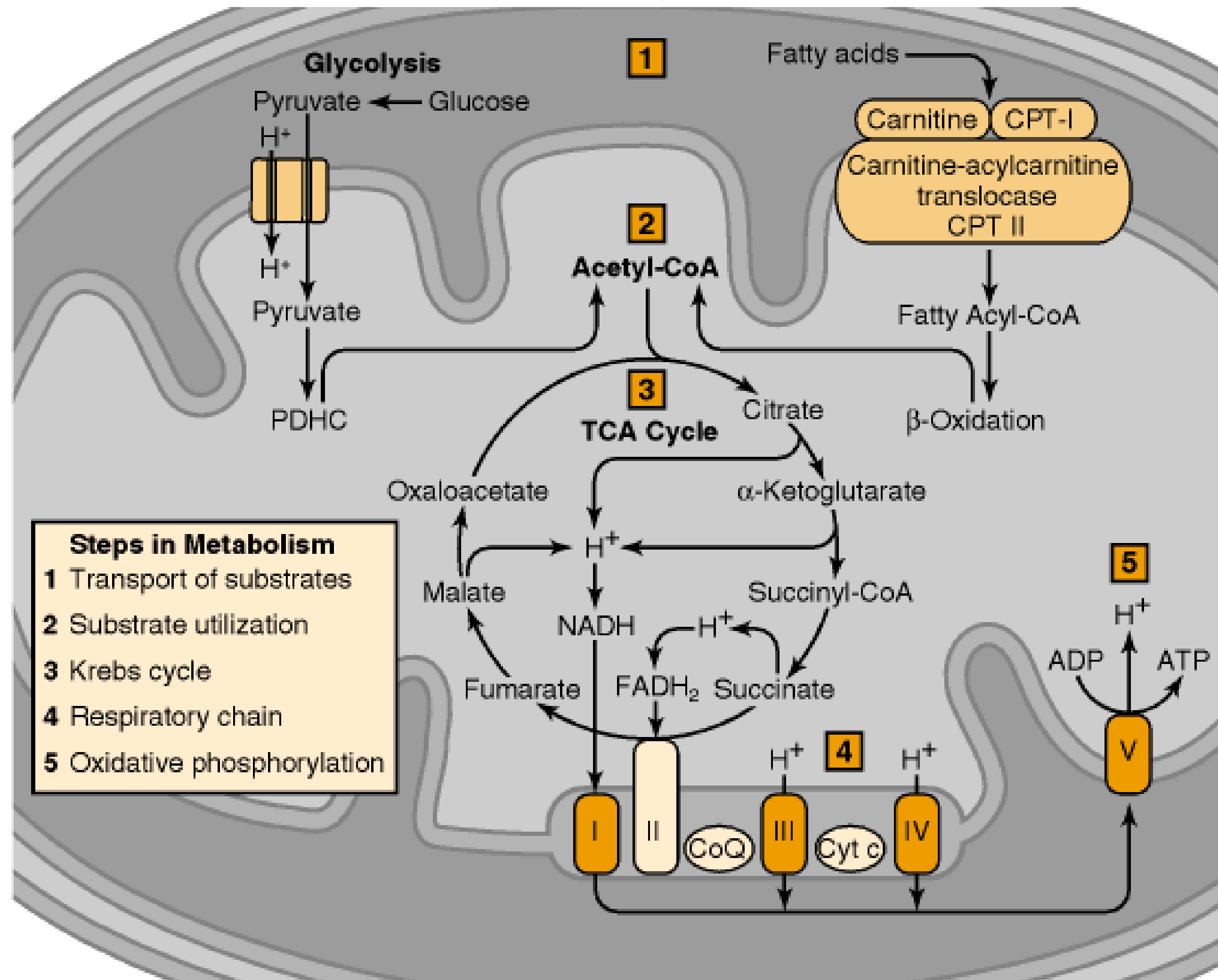
Mitochondrial diseases can be classified by cause as genetic or biochemical.

1. The biochemical classification of mitochondrial diseases

- Genetic classification:
Mitochondrial disease or nuclear disease?
- Biochemical classification:
In which biochemical pathway the defect happened?

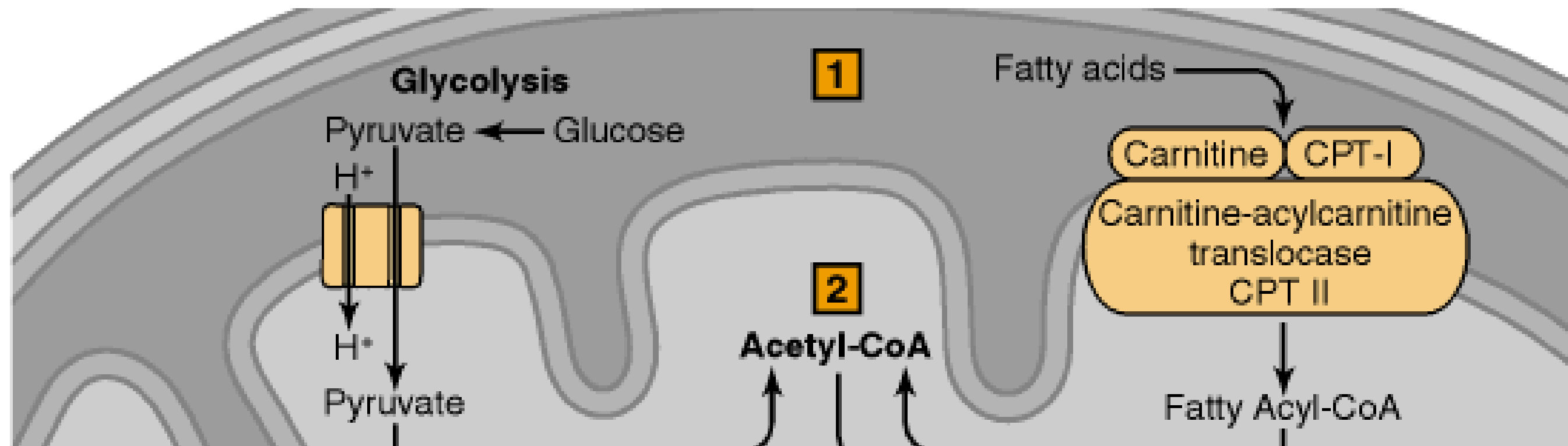
<http://www.ncbi.nlm.nih.gov/books/NBK27914/>

METABOLISM: break down of sugars and fatty acids. When pyruvate/fatty acid enters the mitochondria and gets converted to Acetyl-CoA by (pyruvate dehydrogenase). The transport of pyruvate or the fatty acid could be defective. Or the pyruvate dehydrogenase could also be defective, leading to a defect in substrate utilization or any efficient use of fatty acids and sugars to perform metabolism. Any enzyme from the TCA cycle could also be defective. ETC could contain a defective complex, ATP synthase too.



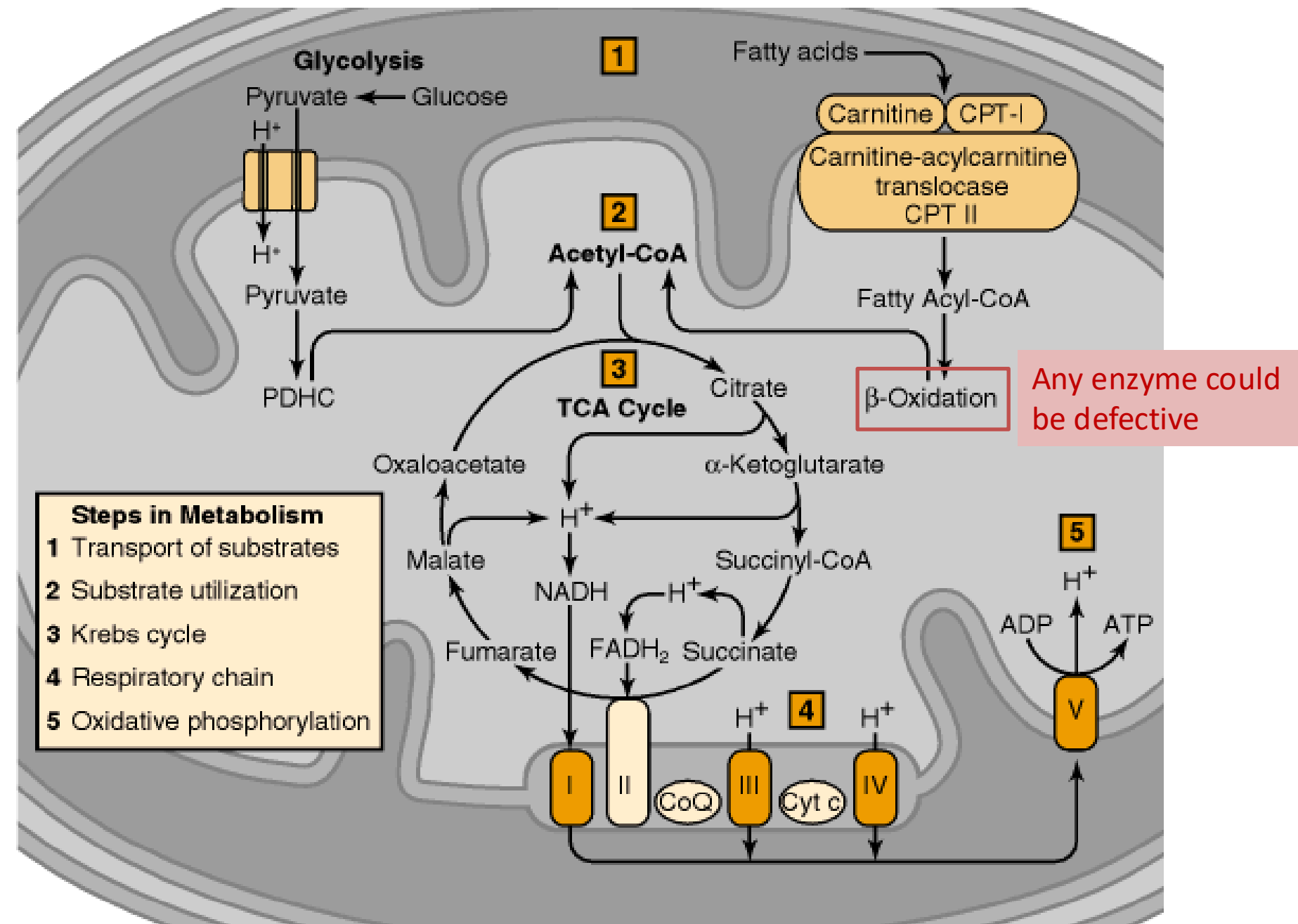
Defects of mitochondrial transport

- interfere with the movement of molecules across the inner mitochondrial membrane, which is tightly regulated by specific translocation systems.



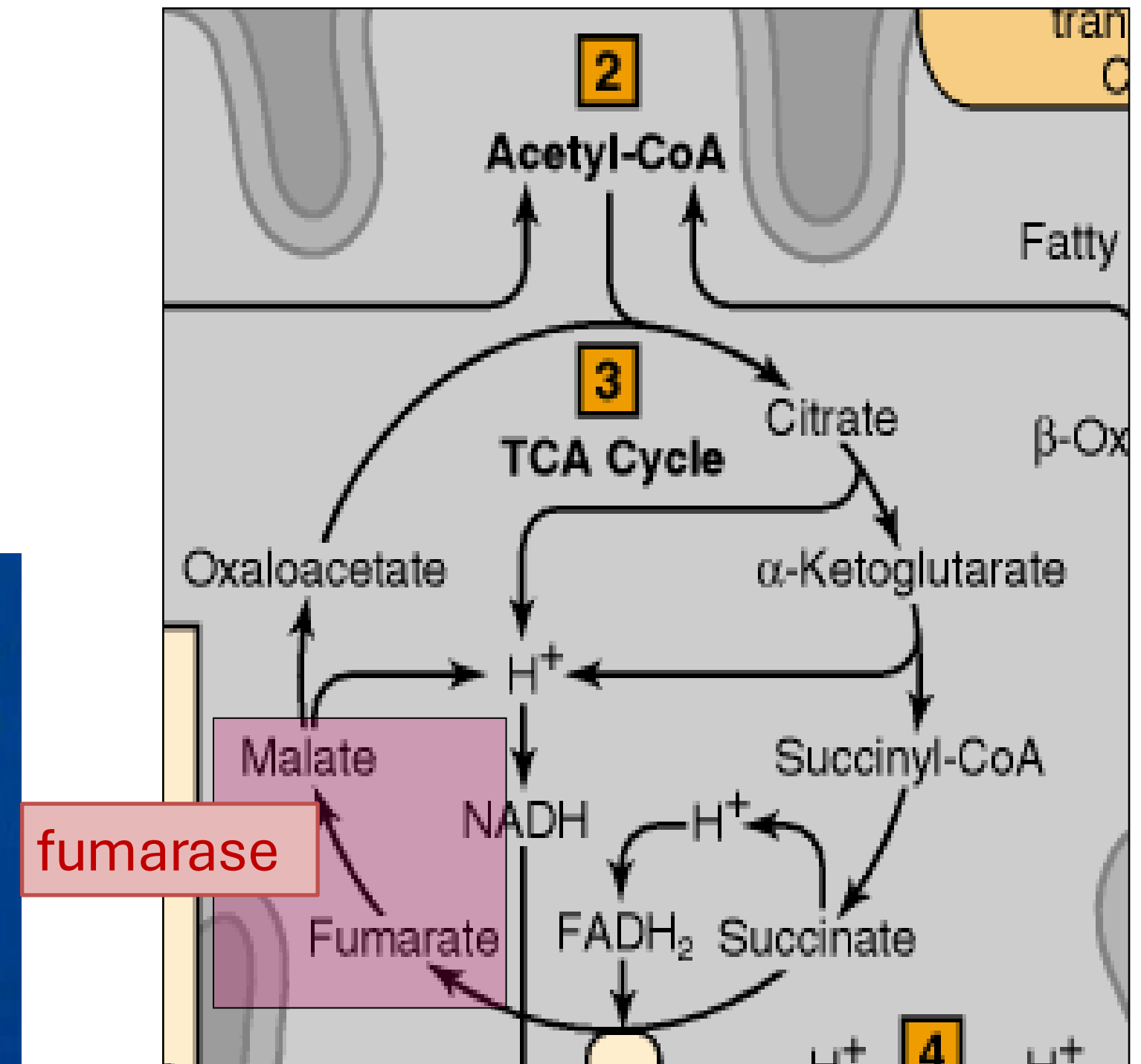
Substrate utilization

- Pyruvate dehydrogenase (PDH) deficiency can cause alterations of pyruvate metabolism.
 - The PDH complex (PDHC) catalyzes the irreversible conversion of pyruvate to acetyl-CoA.
- The most devastating phenotype of PDH deficiency presents in the newborn period.
 - The majority of patients are male, with severe metabolic acidosis, elevated lactate in the blood or CSF, and associated elevations of pyruvate and alanine.
- The defect in the conversion of pyruvate leads to its conversion to lactic acid instead (lactic acidosis in the blood and cerebrospinal fluid).



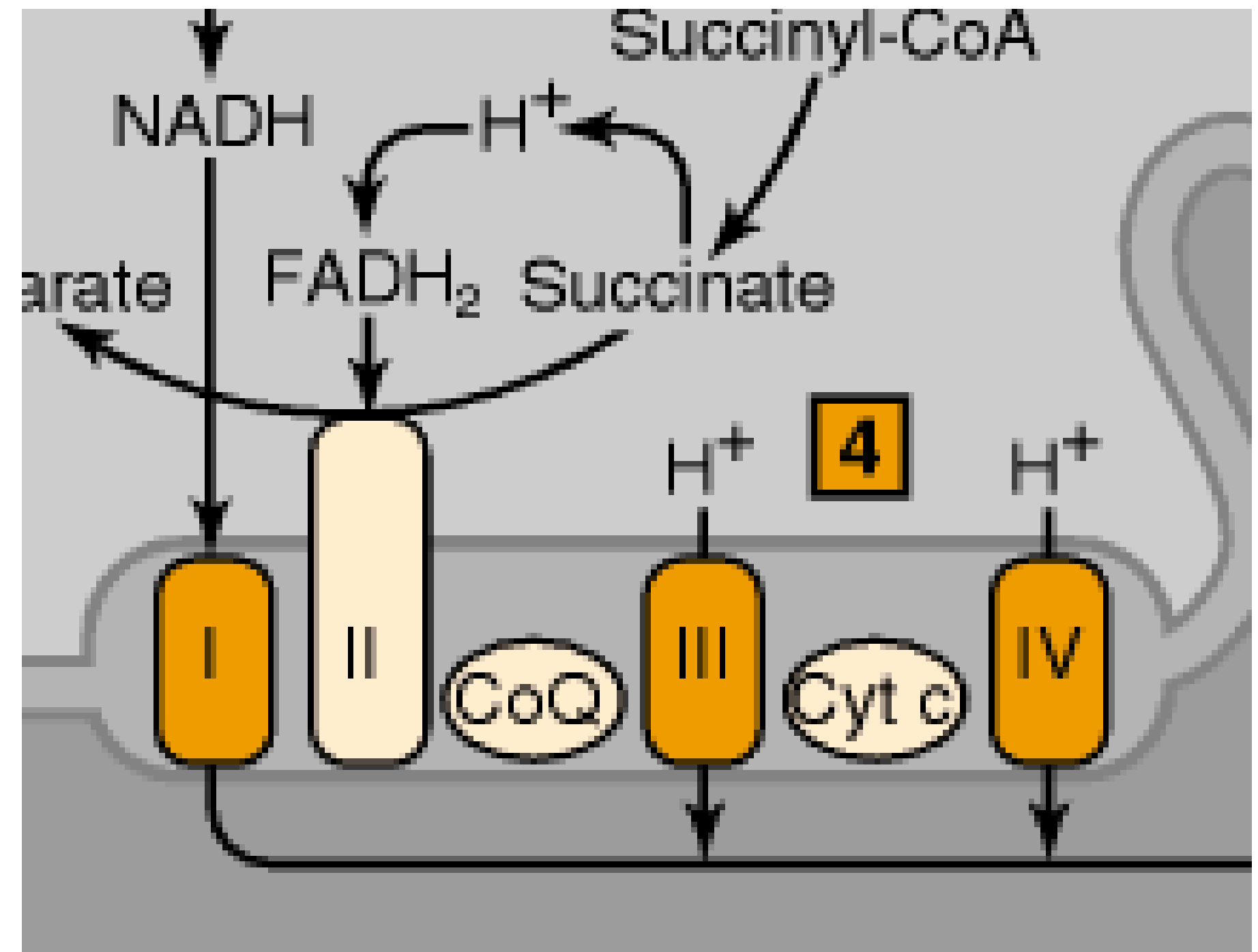
Defects of the Krebs cycle

- Fumarase deficiency is reported in patients having mitochondrial encephalomyopathy.
- **Increases in levels of fumerate and succinate.**
- Features: excretion of large amounts of fumarate and, to a lesser extent, succinate in the urine.
- **Characteristic: relatively small head**



Abnormalities of the respiratory chain reaction

- Defect in any of the 4 electron chain complexes have been reported.
- Defect in any of these complexes, no pumping of the electrons or efficient oxidation for NADH or FADH₂.
- Defect in ATP synthase too, ADP increases and the cell will oxidize more sugars and fatty acids→hyper metabolism and the body heat increases



Defects of oxidation-phosphorylation coupling

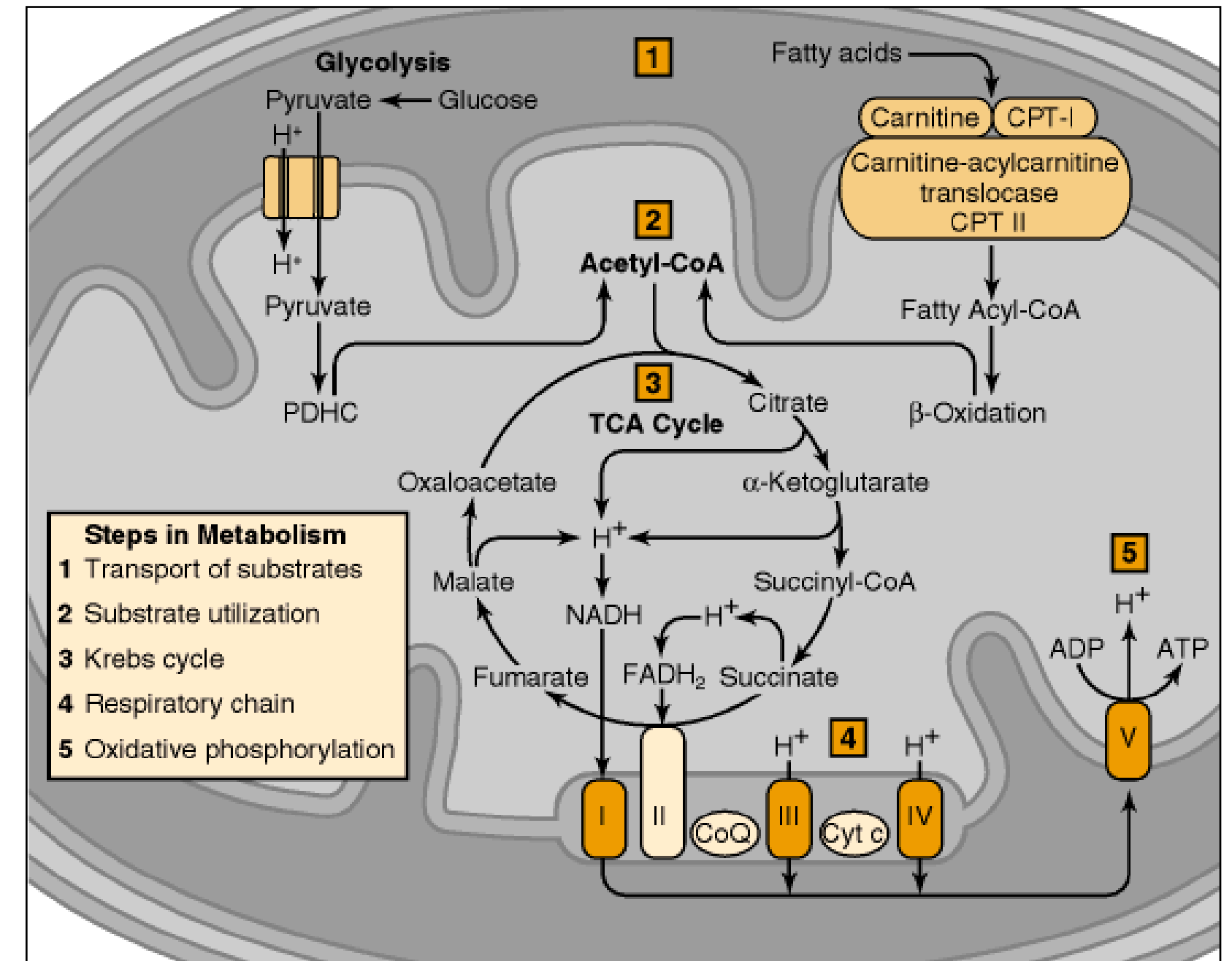
- The best-known example of such a defect is **Luft's disease**, or nonthyroidal hypermetabolism.

Thyroid is responsible for metabolism (cortisol).

Inactive: hypometabolism (increase in weight, storing sugars and fatty acids)

But people with hypermetabolism are often slim.

- Respiratory rate is at a maximal rate even in the absence of ADP, an indication that respiratory control is lost.
- Respiration proceeds at a high rate independently of phosphorylation, and energy is lost as heat, causing hypermetabolism and hyperthermia.



Test yourself !!!!



Additional resources:

References Used:

Prof. Mamoun Ahram recorded lecture

Extra References for The Reader to Use:

اللهم **سخر** لي الأرض **و** من عليها
و السماء **و** من فيها **و** عبادك
الصالحين **و** كل من وليته **أمر**
و ارزقني من حظوظ الدنيا أجمعها
اللهم **أبدل** قلقي **سكينة** وهمي
انشراح **و** خوفي طمأنينة **و** ضيقي
فرح **وعسري** **يسر** **وضروفي** **قوة**
يا رب العالمين
هندروز Hndroz

لا تنسونا من صالح دعائكم

رسالة من الفريق العلمي:

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



Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 8 (Mitochondrial fusion and fission)		Fusion and fission descriptions were swapped
V1 → V2	Slide 15 Autocorrected by mistake	End membrane	Inner membrane

Some grammatical & spelling
mistakes are corrected too