بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 4

Mitochondria

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Lecture 3: Mitochondria and peroxisomes)

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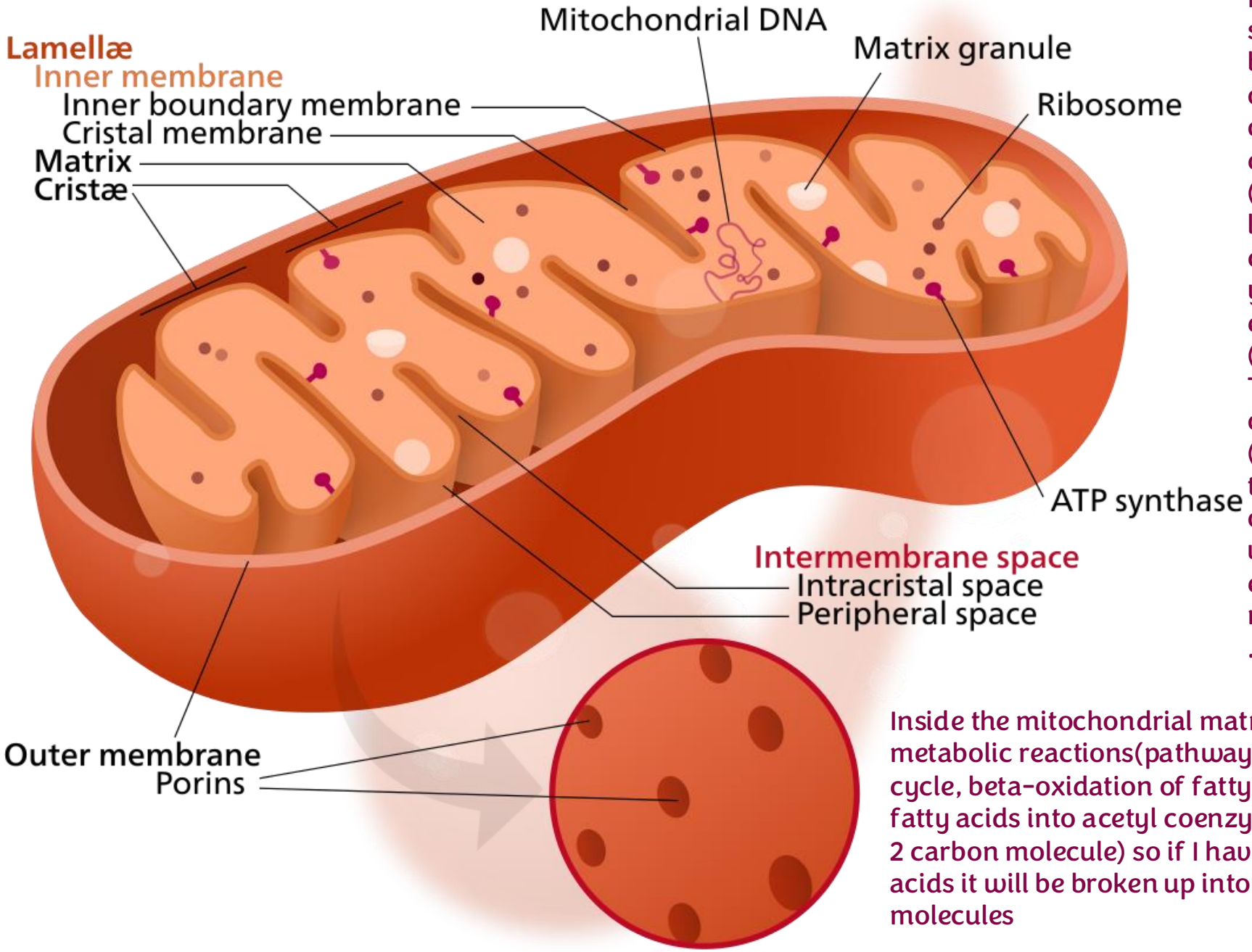
Mitochondria is a very fascinating organelle as it differ from other organelles by its structure. its unique
For example it has an outer and inner membrane(2 membranes system).
Th inner membrane is convoluted (متعرج)its similar to the intestinal membrane to increase surface area



It has a 2 membrane system similar to bacteria . It also has its own genetic system (its own DNA) this DNA is circular its not linear (our chromosomes is linear) also the chromosomes of the yeast (simplest eukaryotes) is linear (multiple chromosomes). The mitochondria has one chromosome (circular) like bacteria, there are multiple copies of this chromosomes, usually 2-10 copies in every mitochondrion(singular) .

Inside the mitochondrial matrix metabolic reactions(pathways) occur eg: krebs cycle, beta-oxidation of fatty acids(breaking fatty acids into acetyl coenzyme A
2 carbon molecule) so if I have 16 carbon fatty acids it will be broken up into 8 acetyl coenzyme A molecules

What are the mitochondria?

All electron transport chain complexes is produced by the mitochondrial DNA.
The mitochondrial proteins are synthesised in the cytosol not on the surface of the ER

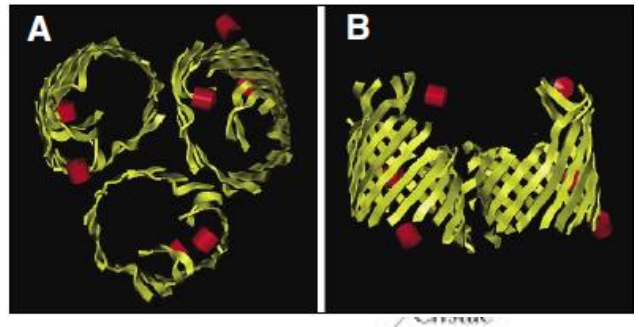
- Mitochondria are specialized organelles that play a critical role in the generation of metabolic energy in eukaryotic cells
  - Generation of ATP from the breakdown of carbohydrates and fatty acids
- They contain their own DNA (typically 2-10 copies), which encodes 37 genes (tRNAs, rRNAs, and 13 mitochondrial proteins).
  - But most mitochondrial proteins (~1500) are encoded by the nuclear genome.
- Most mitochondrial proteins are translated on free cytosolic ribosomes and imported into the organelle.
- They are thought to have evolved from bacteria via endosymbiosis.

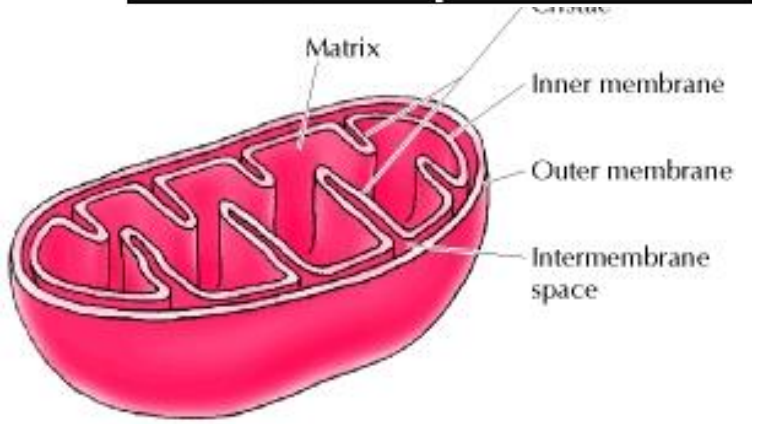
The purpose of mitochondria is to generate energy in the form of ATP. Mitochondrial DNA is small about 16000 base pairs and it codes for 37 genes, those genes get transcribed (production of RNA messenger) some of the mRNA are translated(production of proteins) some are not, those that are not translated are mainly ribosomal RNA which get included in the production of ribosomes , transfer RNA which the short RNA that carries an amino acid and have something called anti-codon. 99% of mitochondrial proteins are made by the nuclear DNA(the main genome)1% of the mitochondrial proteins are made by the mitochondrial DNA those proteins are needed in the electron transport chain (during metabolism transfer of electrons starting from the carriers (NADH, FADH2) them complex to another complex pushing protons outside to the intermembrane space creating proton gradient, then all the protons enter the matrix through the ATP synthase, while entering the ADP converts to ATP

- Since the structure of bacteria and mitochondria is similar so they had this hypothesis that mitochondria was a bacteria billions years ago then it merged with eukaryotic cell during evolution

Structure

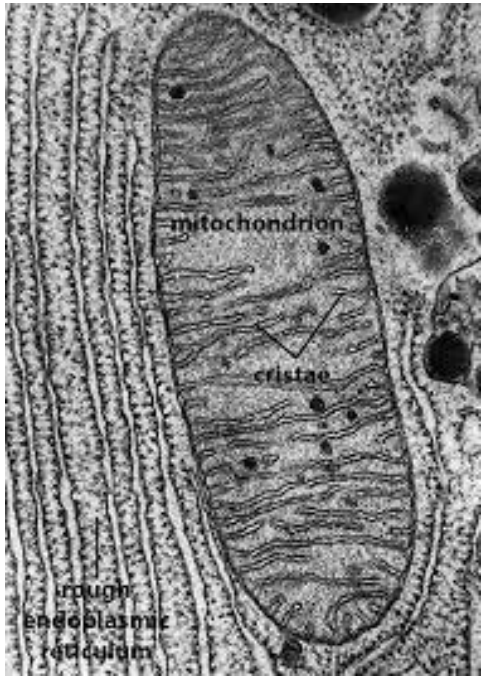
The outer membrane is porous (مفتوح كتير) contains channel proteins called porins
Porins are really large they allow 4 molecules as large as 1000Da to pass through, so nutrients can pass easily through the outer membrane, so the environment of the intermembrane space is similar to cytosol, those molecules cant pass through the inner membrane(barrier)
The inner membrane have a lot of proteins why? To produce a lot of ATP and its folded to increase surface area



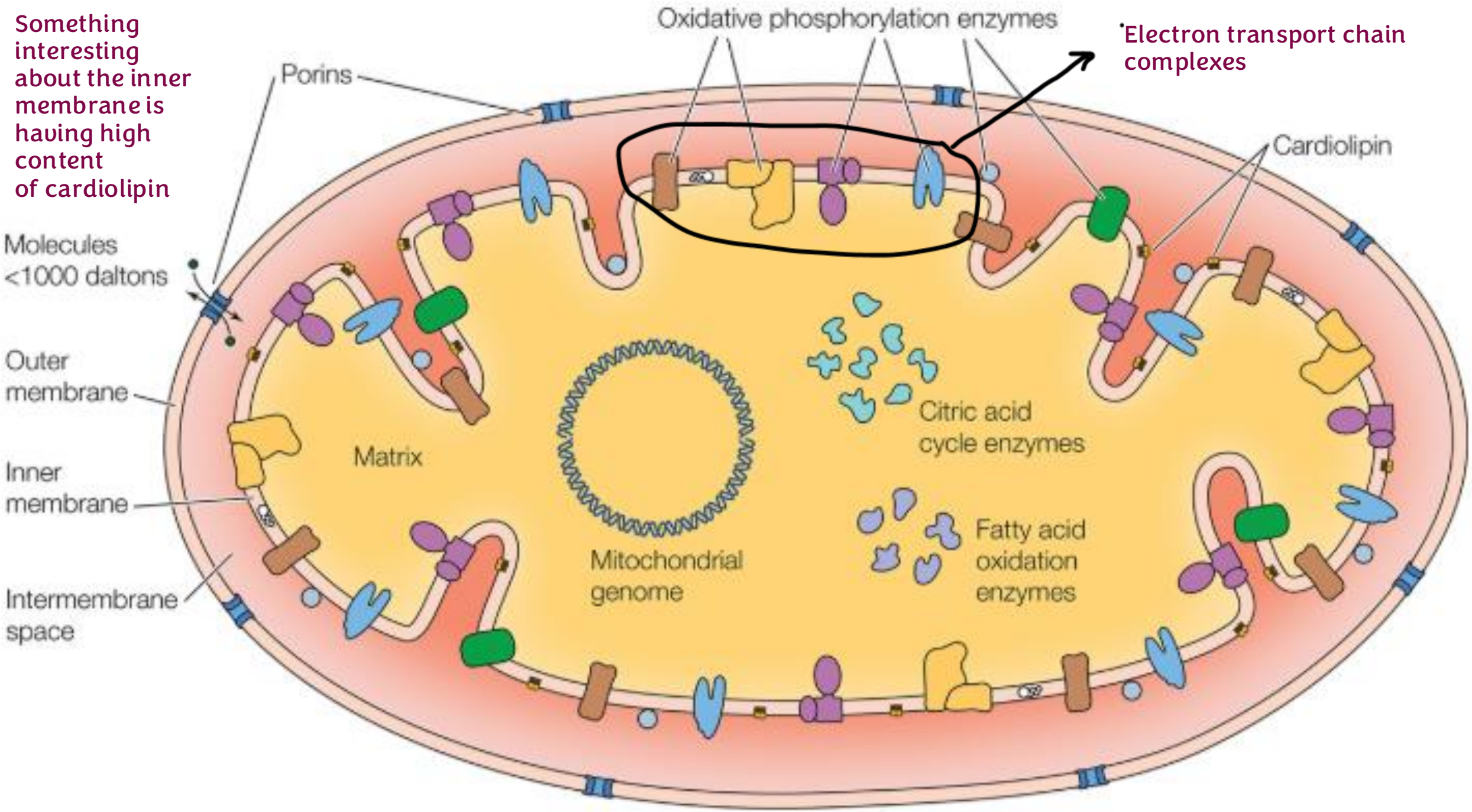


- Outer membrane
  - permeable to small molecules (~1000 Da) because of porins (channel proteins)
- Inner membrane
  - contains a high percentage (>70%) of proteins
  - Forms folds (cristae) to increase surface area
  - Function; oxidative phosphorylation, ATP generation, transport of metabolites
  - impermeable to most ions and small molecules
- Intermembrane space
  - Composition is similar to the cytosol
- Matrix
  - contains the mitochondrial genetic system and the enzymes responsible for the Krebs cycle Where metabolic enzymes are present

- Something is also similar between mitochondria and bacteria are the porins which are B-barrel strands



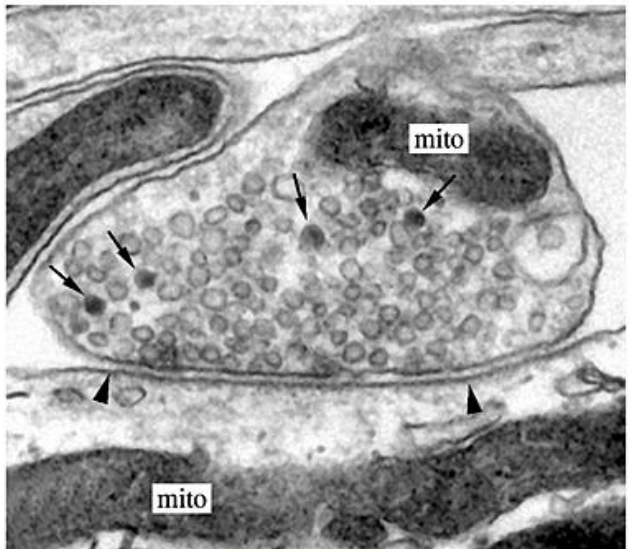
Something interesting about the inner membrane is having high content of cardiolipin

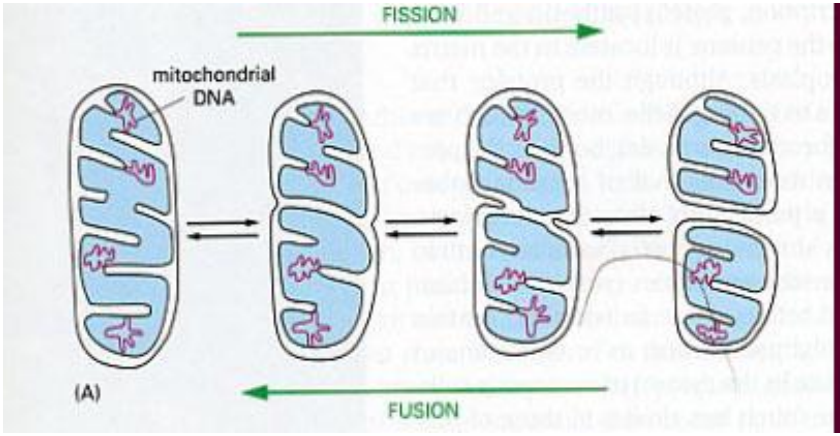


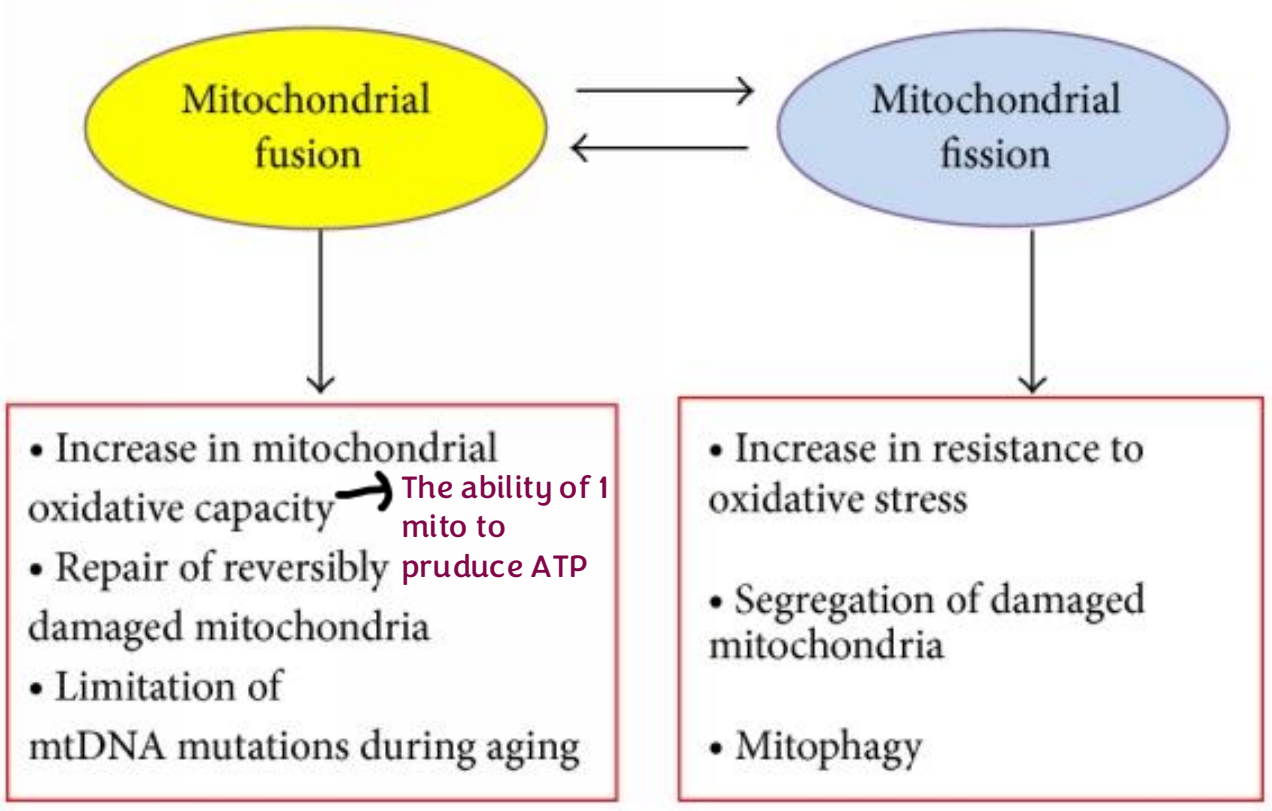
Properties and features

- They are located in cells requiring high-energy use such as synapses.
- They are dynamic (fusion versus fission or division)
  - Exchange genetic material
  - Transfer to daughter cells
  - Regulate autophagy
  - Cell survival and apoptosis
  - Energy demand

Cell death







Mitochondria exists in all cells except RBC, that's why RBC metabolism depends on glycolysis (breaking down glucose to pyruvate). Tissues and cells that require energy have many more mitochondria like muscles have high content of mitochondria compared to other cells. The distribution of mitochondria within cells can be specific, regions inside the cells where energy is needed in high content of mitochondria such as neurons, energy is needed in the periphery the most(synapses).

Mitochondria is dynamic(they move), so they can fuse with each other and they can undergo fission(division)
So one mitochondrion can become 2
Why are they dynamic ? Because the genetic material is exchanged when fusion and fission happens this aids the transfer of mitochondria to daughter cells
Mitochondria is important because it regulate autophagy (self eating)

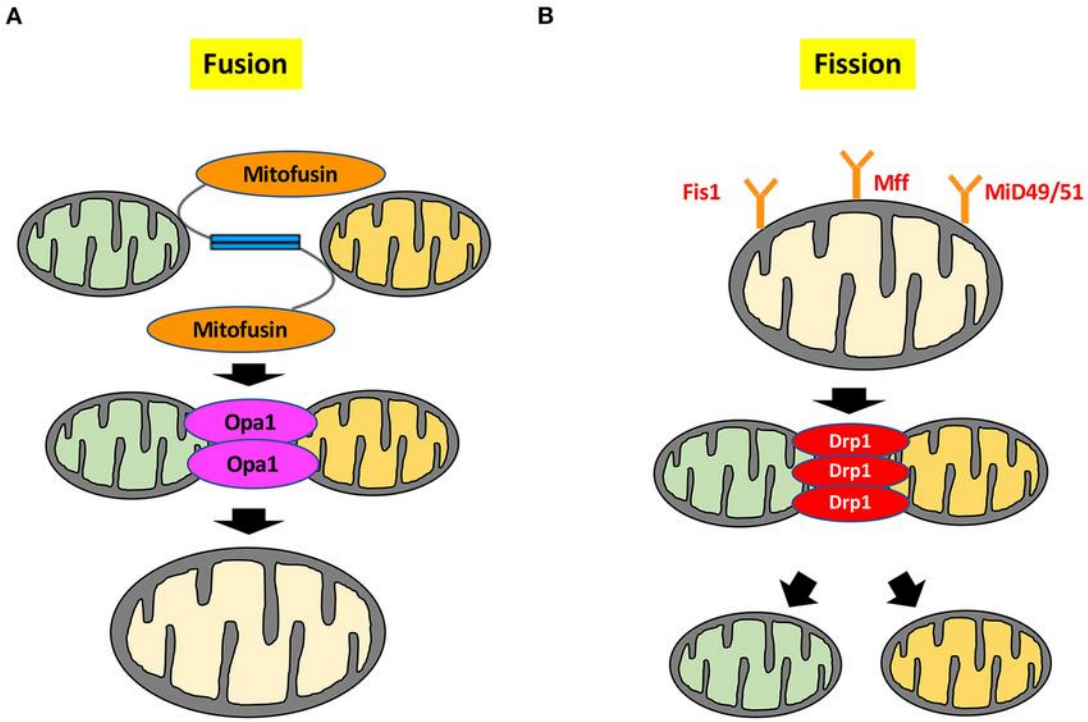
You can increase the efficiency by fusing different cells, when muscle cells needs a lot of energy it divides the mitochondria to produce energy as well so fission and fusion can increase the production of energy but in different circumstances (in different cells)
There is no DNA repair in mitochondria, so by under going fusion or even fission you can remove the mitochondrion that contain damaged DNA and this goes through autophagy (its eliminated), this how the cell protects itself from the damaged mitochondria

The molecular mechanisms of fusion/fission

Fusion is regulated by multiple proteins but we'll focus on 2 proteins (mfn1 and opa1) they binds to GTP and converts it to GDP

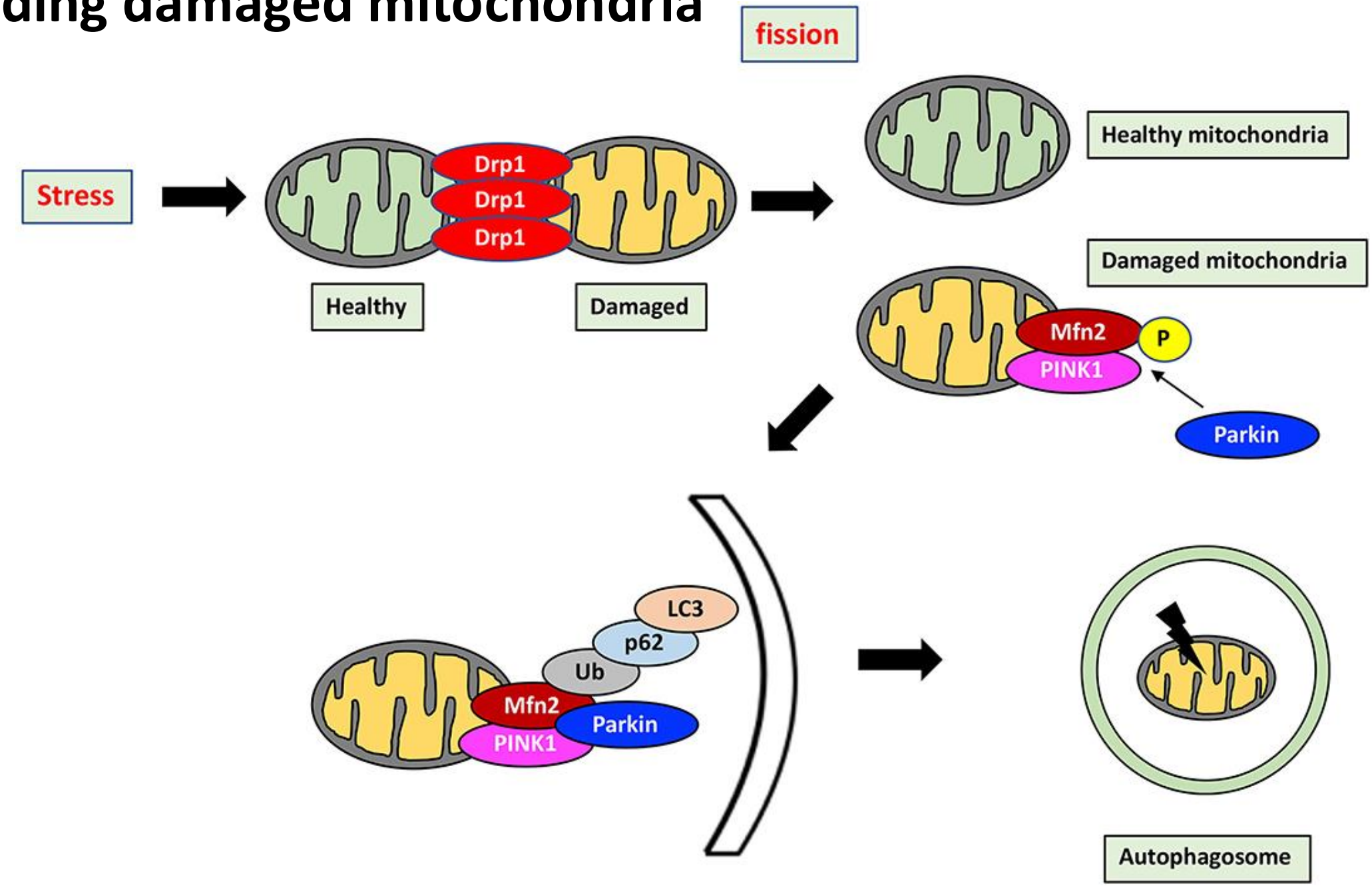
- Mitochondrial fusion is driven by GTPase proteins, Mfn1 and Opa1.
- Mfn1 is responsible for the fusion of the outer membrane, whereas Opa1 then mediates fusion of the inner membranes.
- Mitochondrial fission is mediated by a third GTPase called Drp1, which assembles into a ring structure around a mitochondrion,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

mitofusion



Drp1 is important for fission

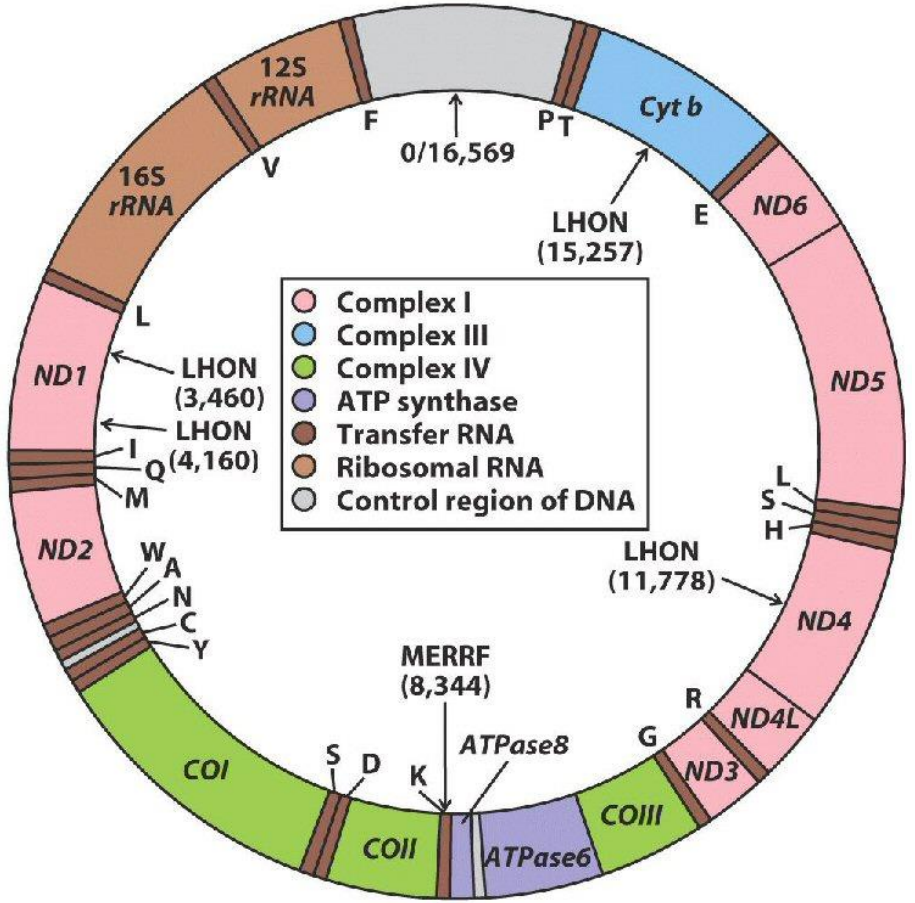
Discarding damaged mitochondria



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.

Mitochondrial genome

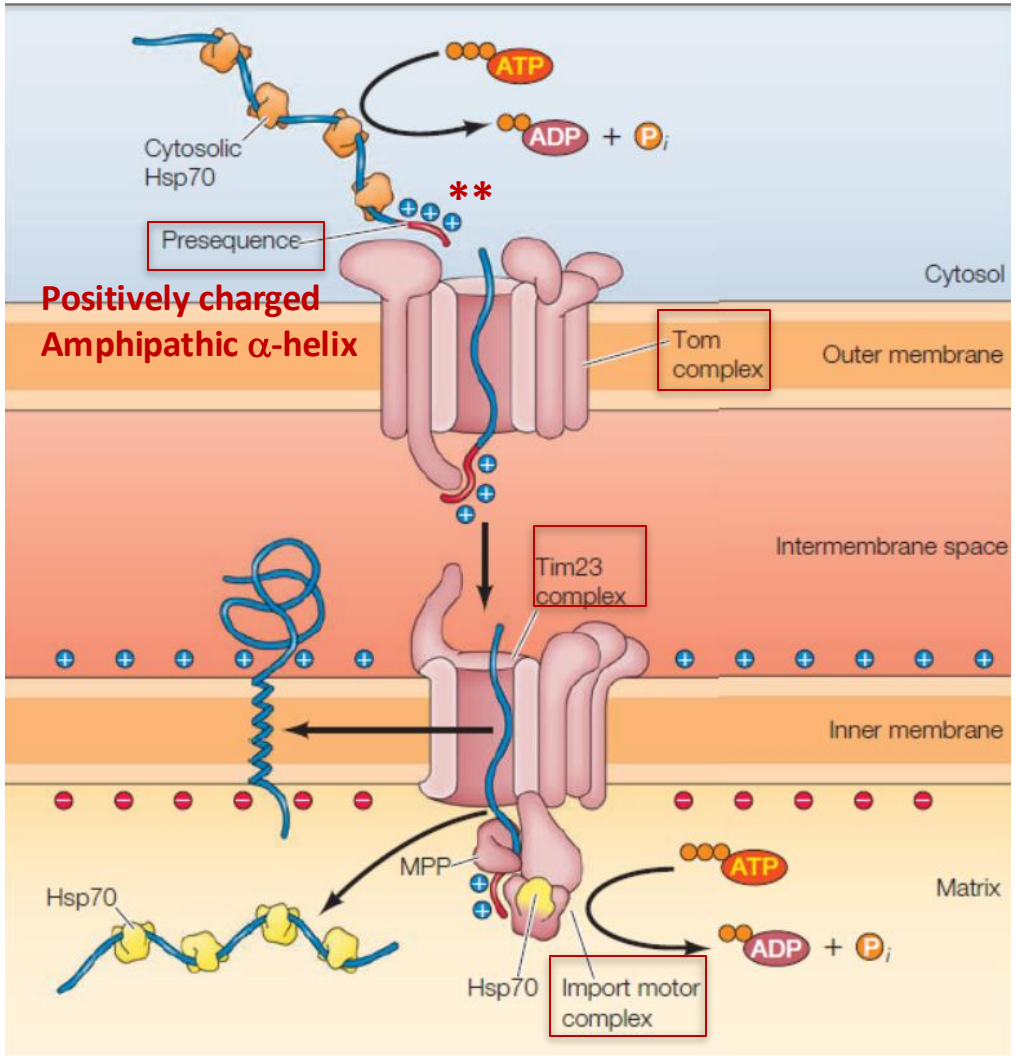


Mitochondrial proteins

- 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) 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 (translocase) called the **Tom complex** on the outer membrane followed by passing through another channel (translocase) called the **Tim complex** in the inner membrane.
- 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**.

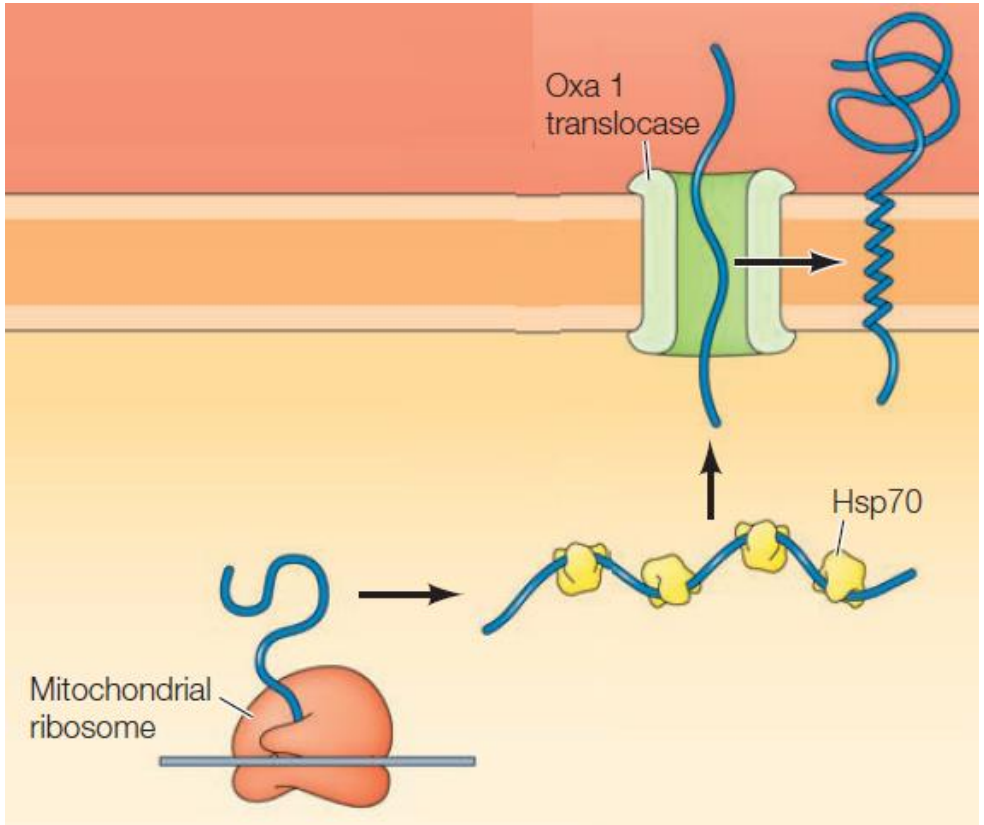


- Protein Synthesis occurs in cytosol, and then the polypeptide is transported from the cytosol inside the mitochondria .what is the code?this is the mitochondrial protein!! في عنا سلسله موجودة على الN terminal of polypeptide and we call it **presequence** (sequence of specific amino acids) this that make the cell know that this the mitochondrial protein so the mitochondrial polypeptide goes into the mitochondria .
- Tom complex (a channel protein allows the polypeptide to pass through the outer mitochondrial membrane into the inner membrane space)
- Tim complex (a channel protein helps the polypeptide pass through inner membrane into the mitochondrial matrix)
- Inside the mitochondrial matrix the presequence removed and polypeptide folds into its functional 3d structure

- If the protein its so important to be part of the outer or inner membrane, what will happen in this case? As the polypeptide moves through the Tom complex if the transmembrane domain a pairs if it choose up ,the Tom complex recognize it and as the polypeptide moves through the protein its pushed a side into the membrane, Tom complex pushes a side وهو عماله يدخل بيجي عال polypeptide so it is become part of the outer membrane same thing with the Tim complex when they watch there a transmembrane domain push into the inner membrane, so the protein will be part of inner or outer membrane, Otherwise it enter inside the mitochondrial matrix presequence is cleaved and protein folding that is it 😃

Targeting of inner membrane proteins

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



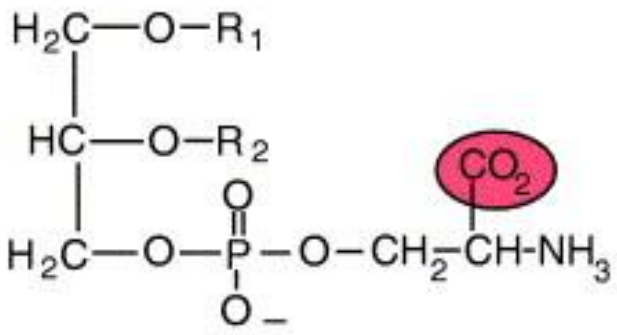
These protein for elecrton transport chain we said that they will be uncoded by the mitochondrial genome هذا يعني بصيرلهم production,transcription and translation, production of mRNA then translation into polypeptide inside the mitochondrial matrix . Will happen production of the polypeptide inside the mitochondrial matrix and then certain (we aren't required to know it)take the polypeptide into the oxa translcase and it takes this protein and insert it inside the inner membrane

Mitochondrial phospholipids Phosphatidyl…

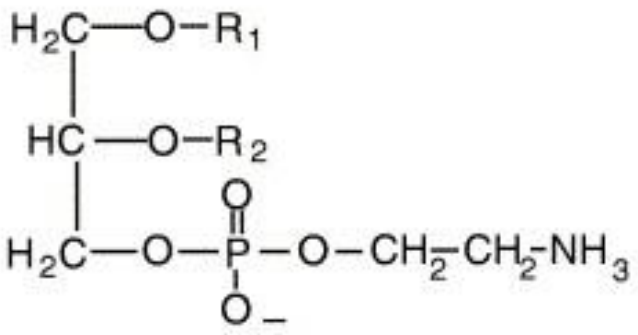
- Phosphatidylcholine and phosphatidylethanolamine are synthesized in the ER and carried to mitochondria by proteins.
- Phosphatidylserine can then be synthesized from phosphatidylethanolamine in the mitochondria.

These are glesrofattyacid because the back bone it's a glesrol

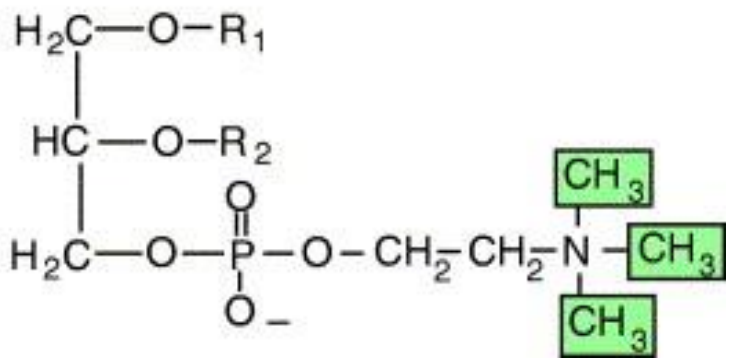
Phosphatidylserine



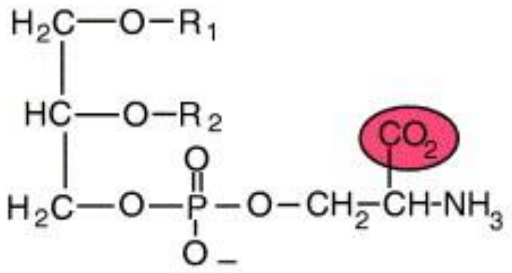
Phosphatidylethanolamine



Phosphatidylcholine

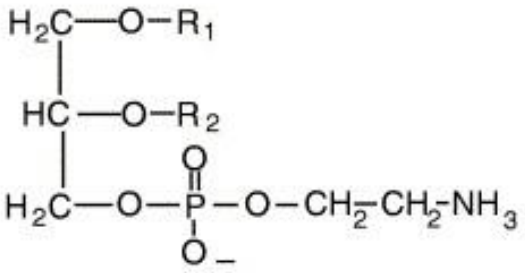


Phosphatidylserine



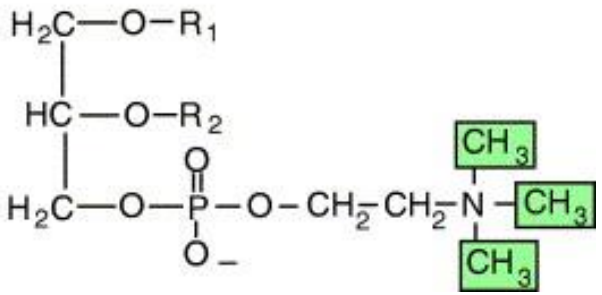
We put fatty acid at the first and second OH in the third one we put phosphate group that's why we called it phosphoglesrolipid then we put a head group these group could be ethanol,amine or choline or serine or inositol

Phosphatidylethanolamine



Its consist of two carbon and amino group, that's why two carbon متل الايثيل with amino group

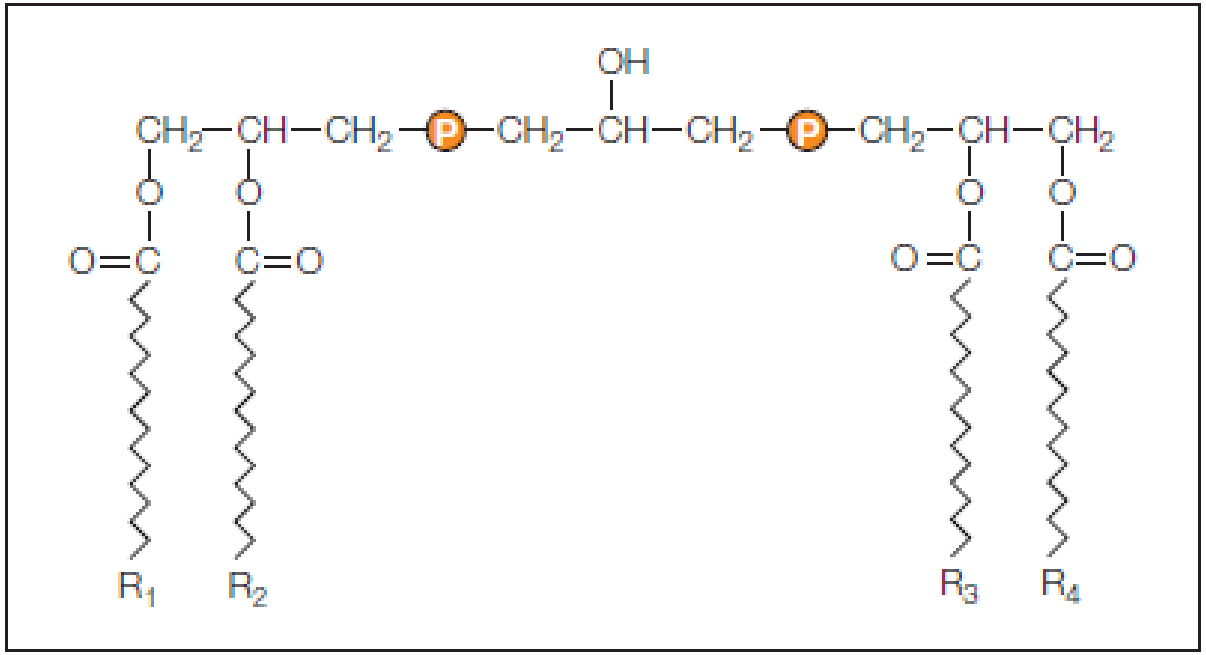
Phosphatidylcholine



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

Mitochondrial phospholipids Cardiolipin

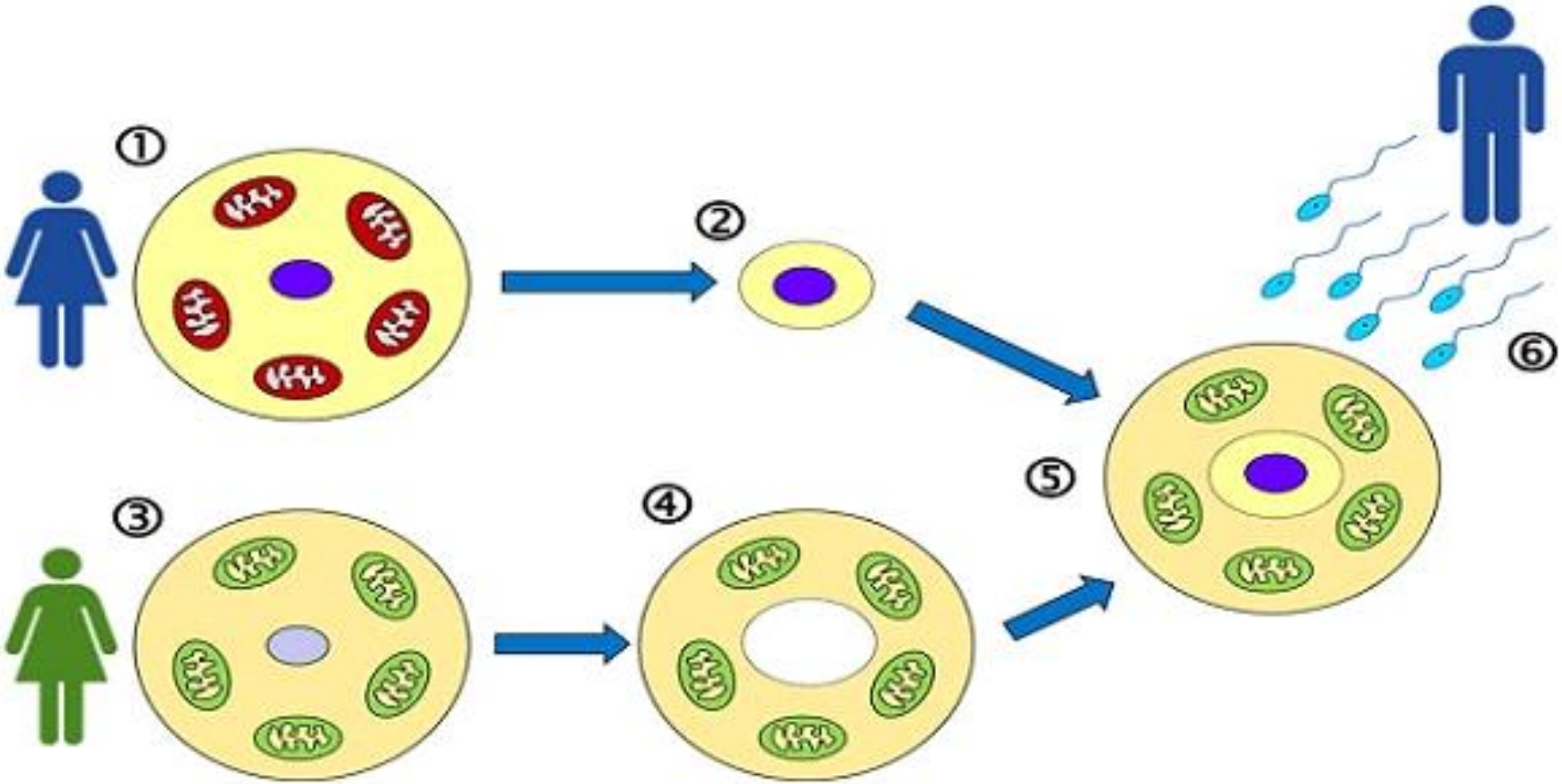
- The unusual phospholipid, cardiolipin, which contains four fatty acid chains, is also synthesized in the mitochondria.
- This molecule improves the efficiency of oxidative phosphorylation by restricting proton flow across the membrane.
- It is also involved in the mitochondrial dynamics of fusion and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



Defects of nuclear DNA

- The vast majority of mitochondrial proteins are encoded by nuclear DNA.
- All areas of mitochondrial metabolism can be affected.

Mitochondrial Replacement Therapy



Not secure | nationalpost.com/news/world/jordanian-couple-has-baby-using-three-parent-genetic-engineering-but-its-actually-abou

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*The **British**-developed technique was performed in **Mexico** by a **Chinese-American** physician who worked in New York*

Jordanian couple has baby using 'three parent' genetic engineering — but it's actually about 2.001 parents

The Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques, although the procedure is illegal in most countries

This Jordanian newborn represents the first successful birth in a new wave of “three parent” techniques — ones that are more sophisticated, and that will likely stick around much longer.

رسالة من الفريق العلمي:

بدأ عامٌ جديد ، وبدأت حكايةٌ أُخرى سنكون فيها أبرز الشُخوص .
ستتولى الأقدار تحديد الأماكن والأزمان ، غير أنه سيقع على عاتِقِنا اختيارُ الشُركاءِ . فَأحسِنُوا صُنعاً ، فَالناس كالمعادن تكشفهم الأزمانُ، هذا لطيفٌ أبيضُ القلبِ ، وهذا لَئيمٌ قبيحُ الروح .
واستَذكِرُوا دوماً حين يلمع من حولَكم البريقُ وتتكاثَرُ الأضواءَ ، أنّ ليسَ كلٌّ ما يلمع ذهباً، والاقتراب من الأشياء يُبرز عِللها ويُبدد انبهار البدايات.
يمكننا ان نميل شيئاً بسيطاً ، ولكن سيملِكُنا الانحراف، بينهما قرارٌ ويبعِدُهُما خُطوة .
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لجين القاضي

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Corrections from previous versions:

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