Lecture 3: bioenergetics and metabolism (mitochondria and peroxisomes)

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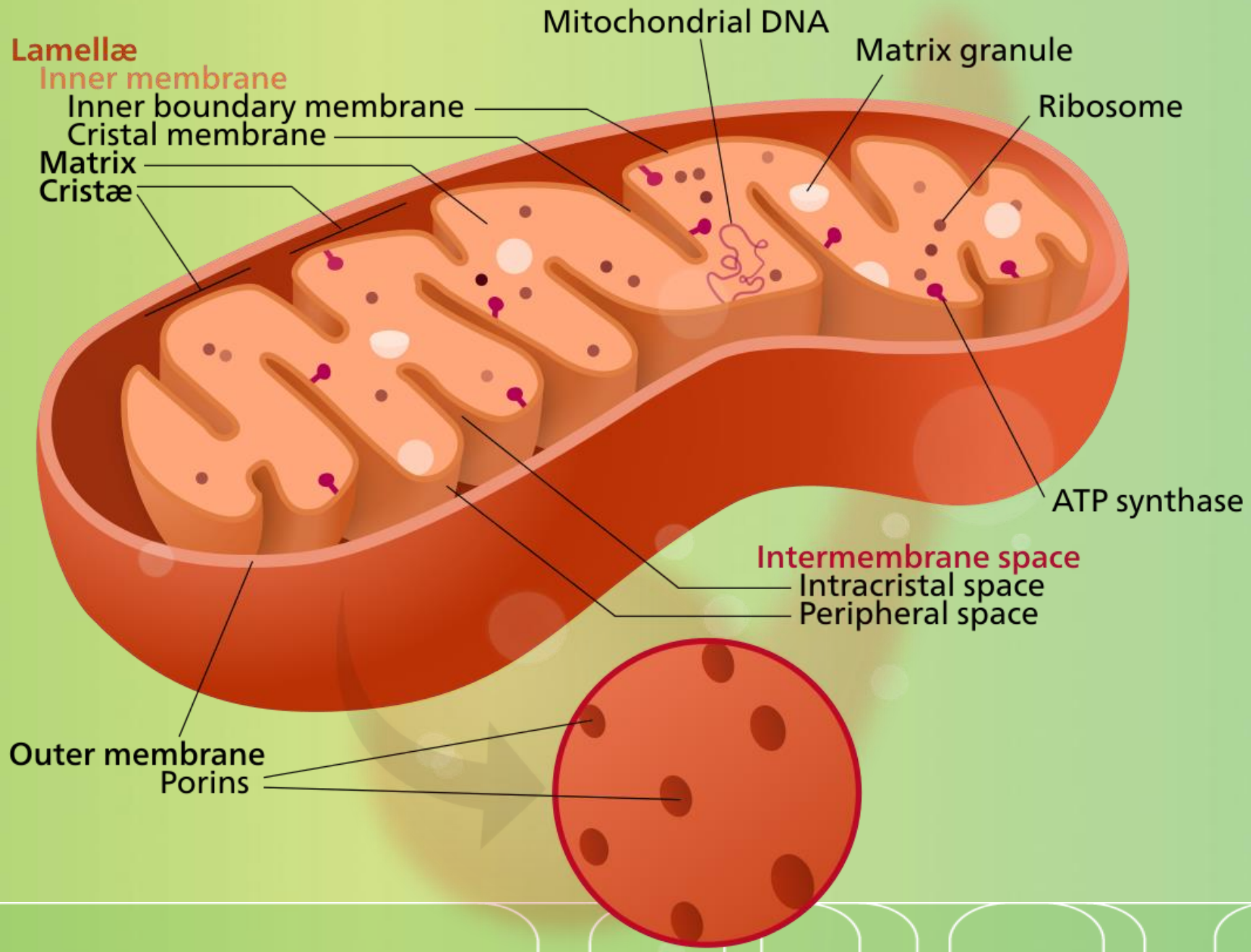
Second year, First semester, 2024-2025

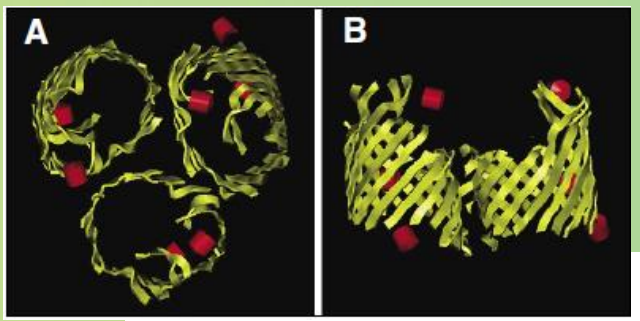

Lamellæ
Inner membrane
Inner boundary membrane
Cristal membrane
Matrix
Cristæ
Mitochondrial DNA
Matrix granule
Ribosome
ATP synthase
Intermembrane space
Intracristal space
Peripheral space
Outer membrane
Porins

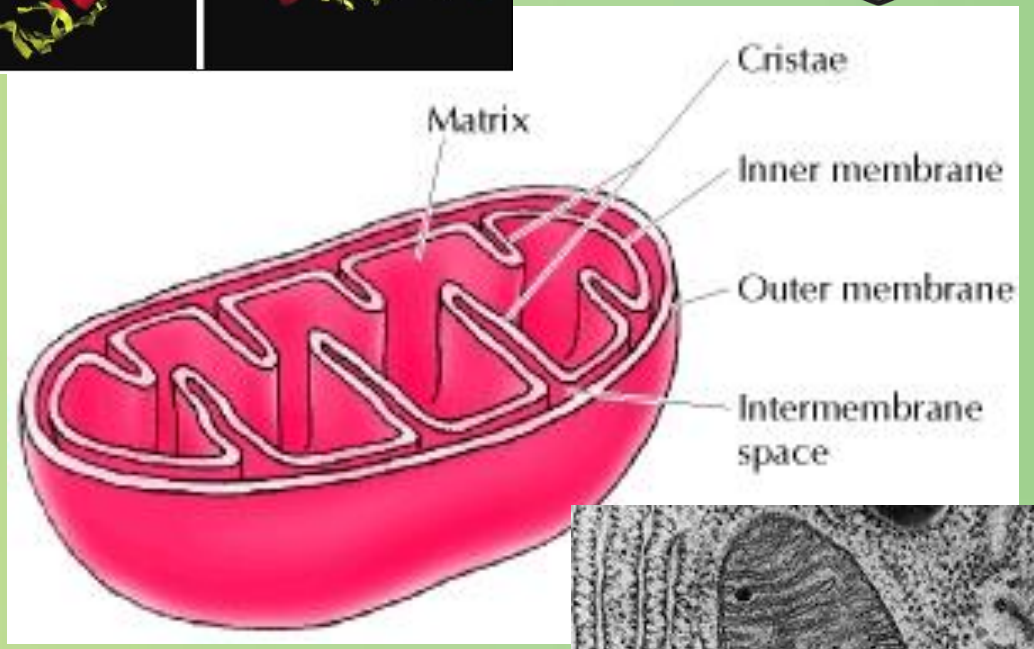
What are the mitochondria?

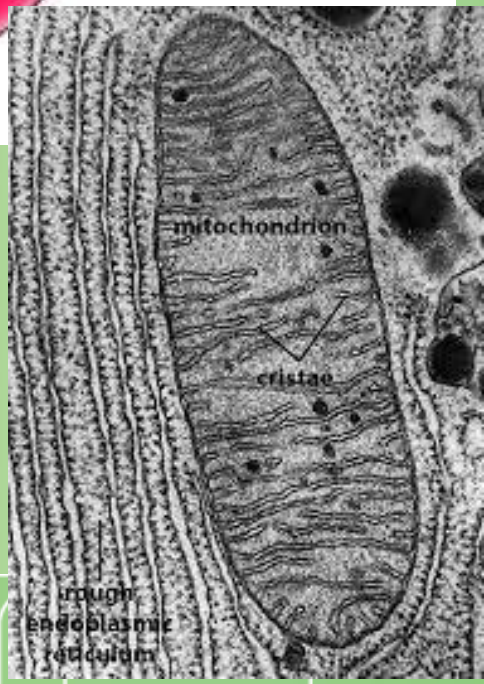
- Mitochondria are thought to have evolved from bacteria via endosymbiosis.
- They play a critical role in the generation of metabolic energy in eukaryotic cells
  - Generation of ATP from the breakdown of carbohydrates and fatty acids
- They contain their own DNA, which encodes tRNAs, rRNAs, and 13 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.

Structure

- 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

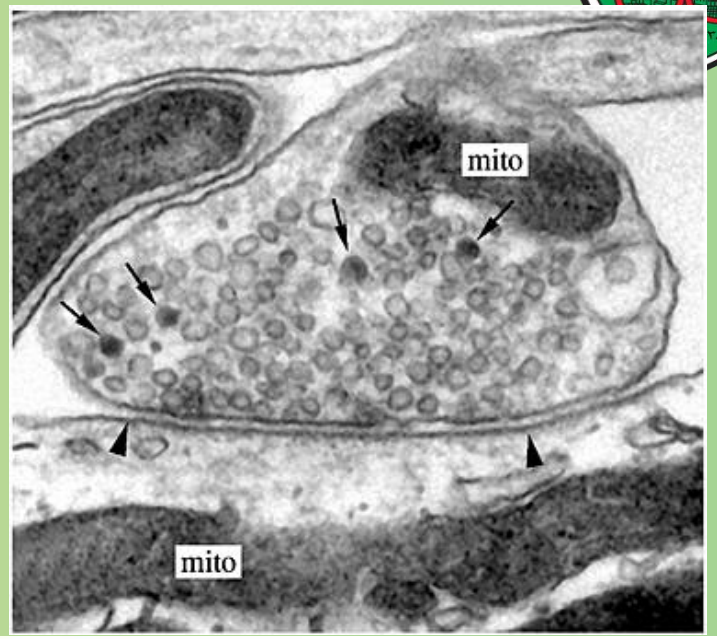


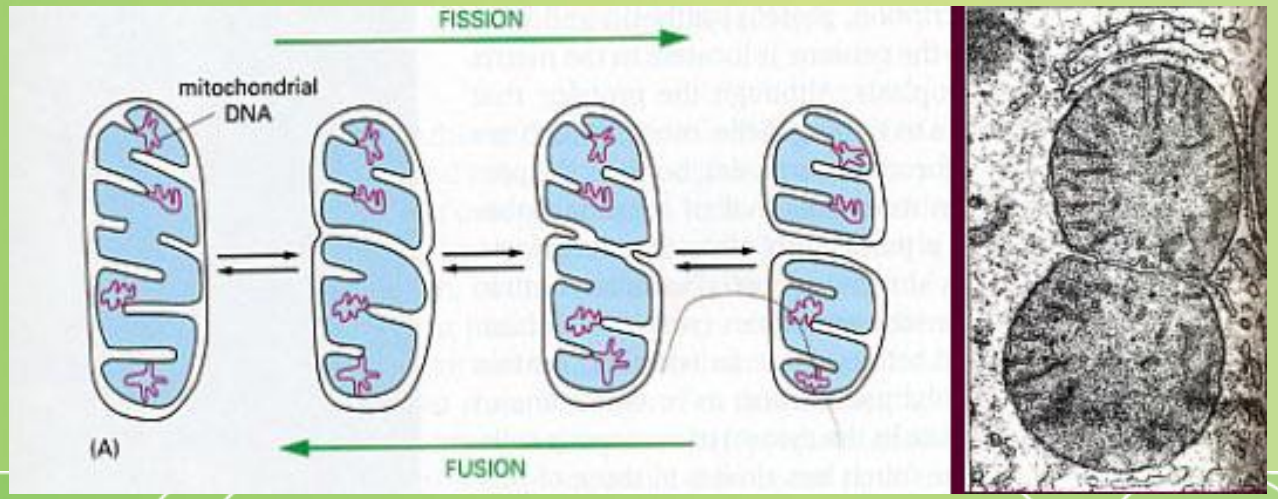


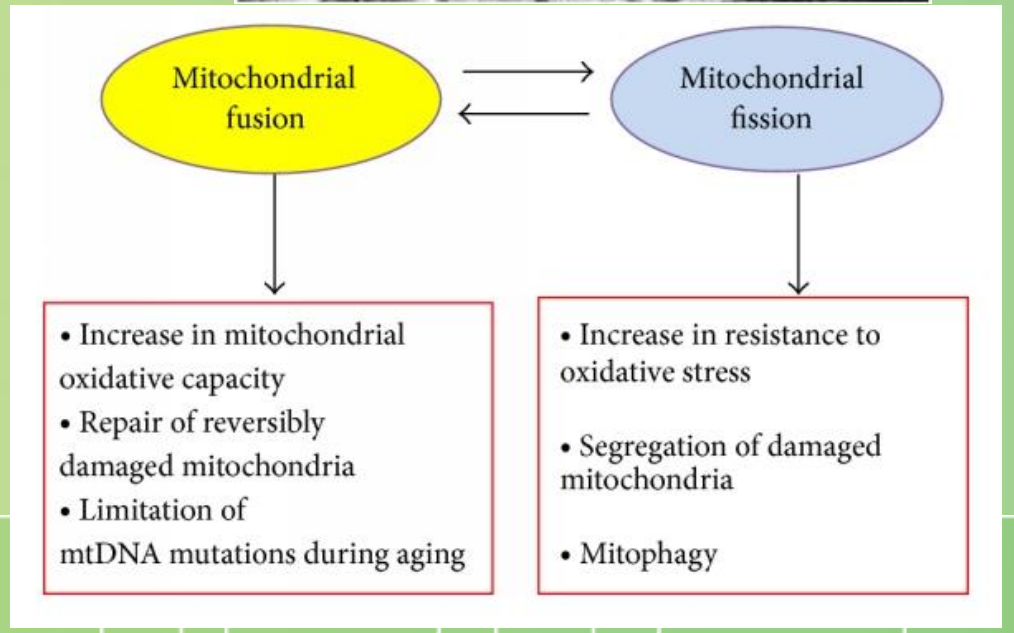


Properties and features

- They are located in cells requiring high-energy use such as synapses.
- They are dynamic (fusion and division)
  - Exchange genetic material
  - Regulate autophagy
  - Cell survival

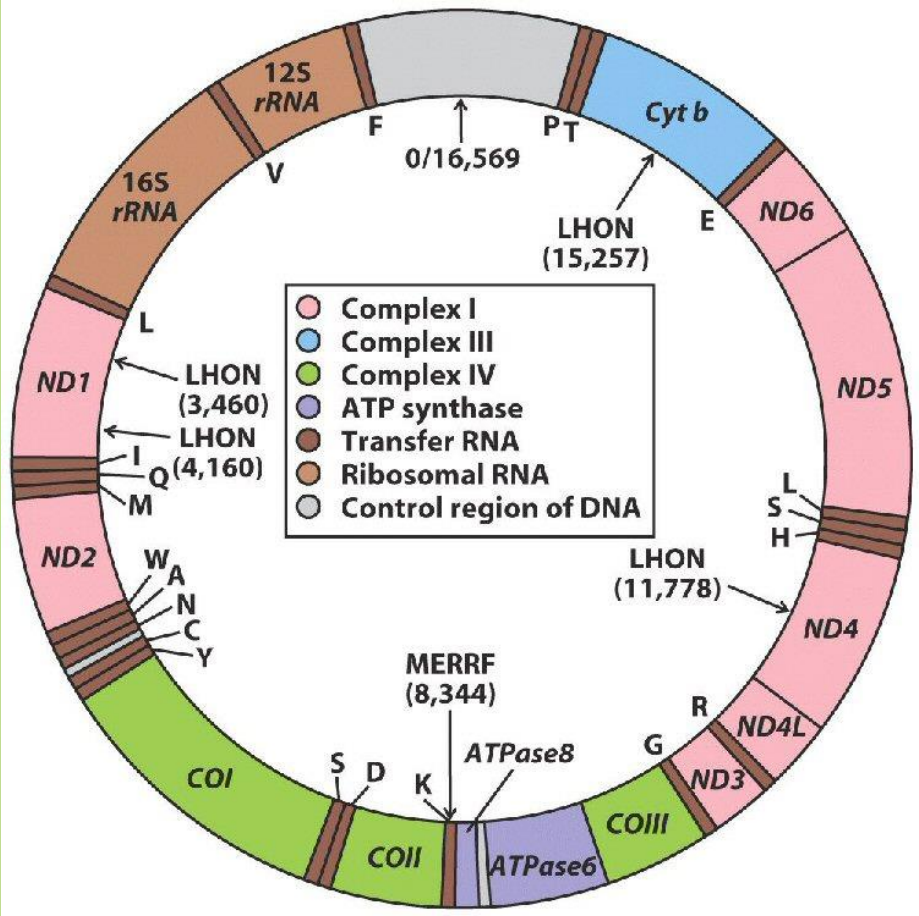






The Genetic System of Mitochondria

- 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.

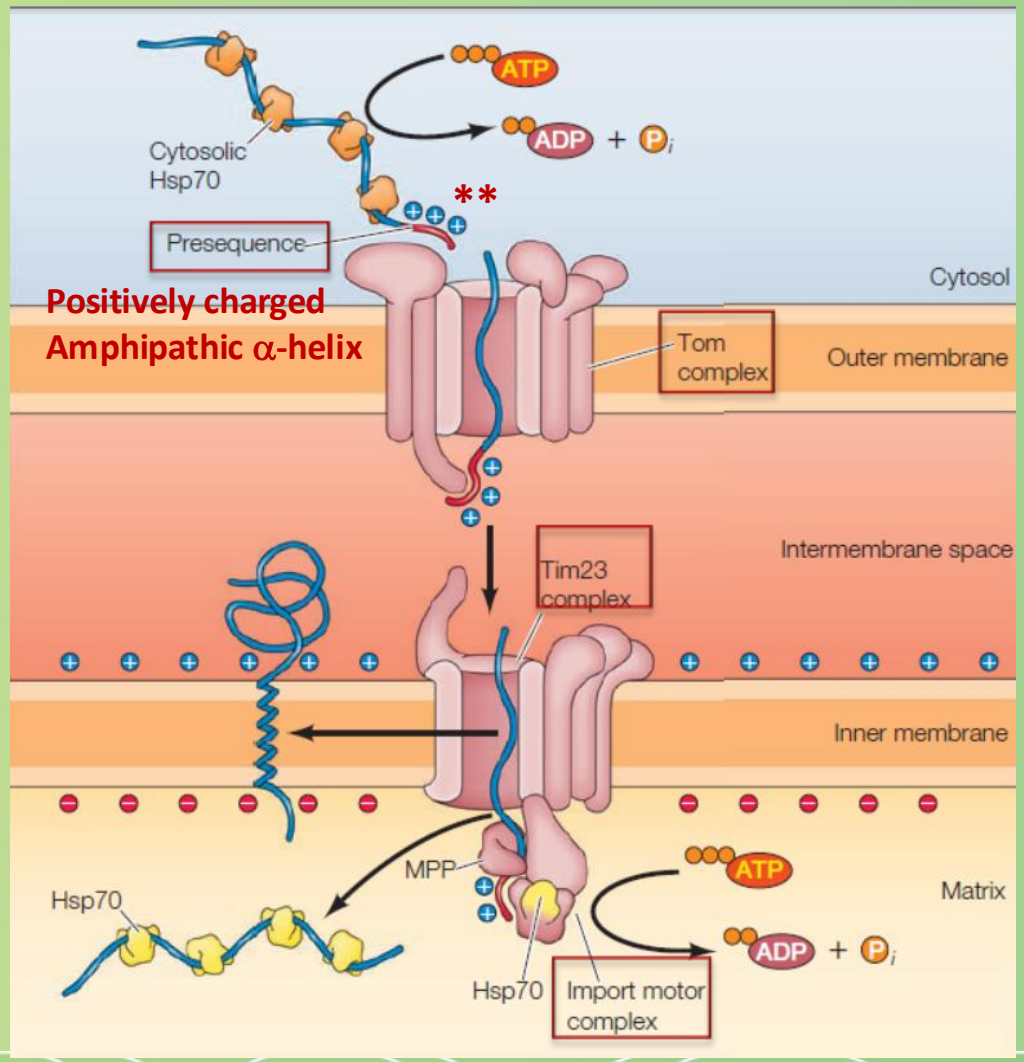


Mitochondrial proteins

- 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.

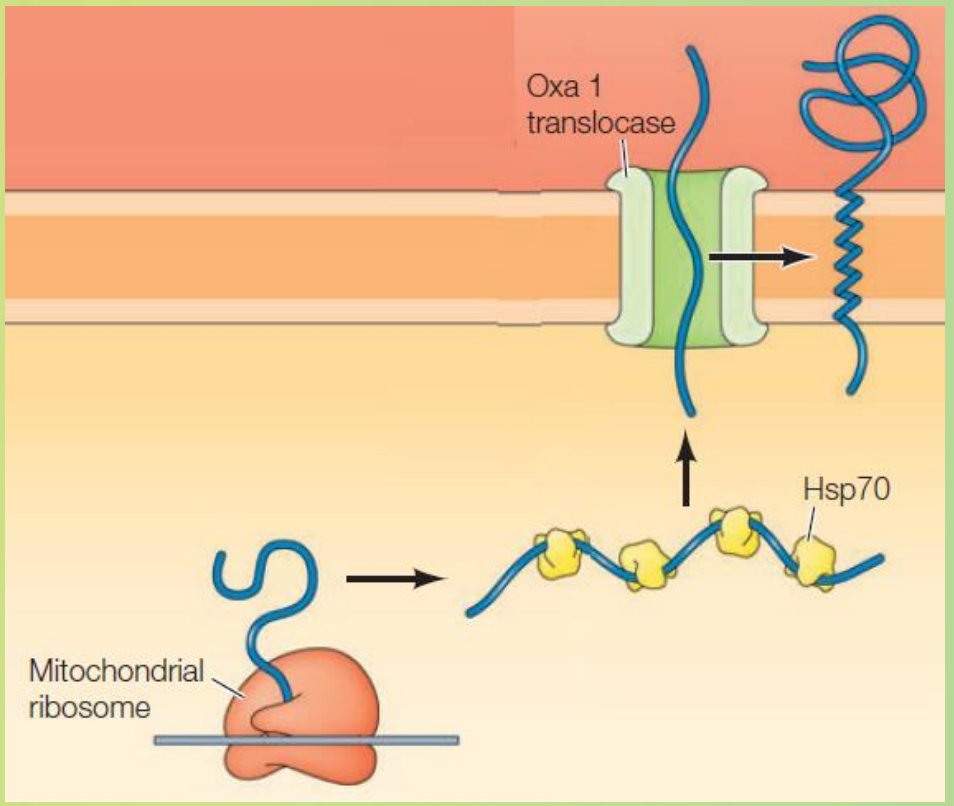
Protein Import and Mitochondrial Assembly

- 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**.



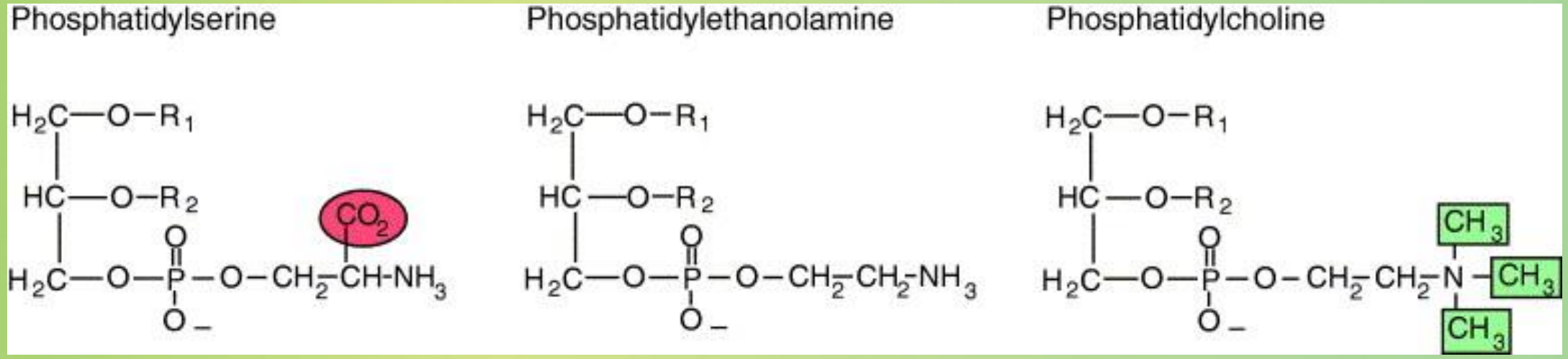
Targeting of inner membrane proteins

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



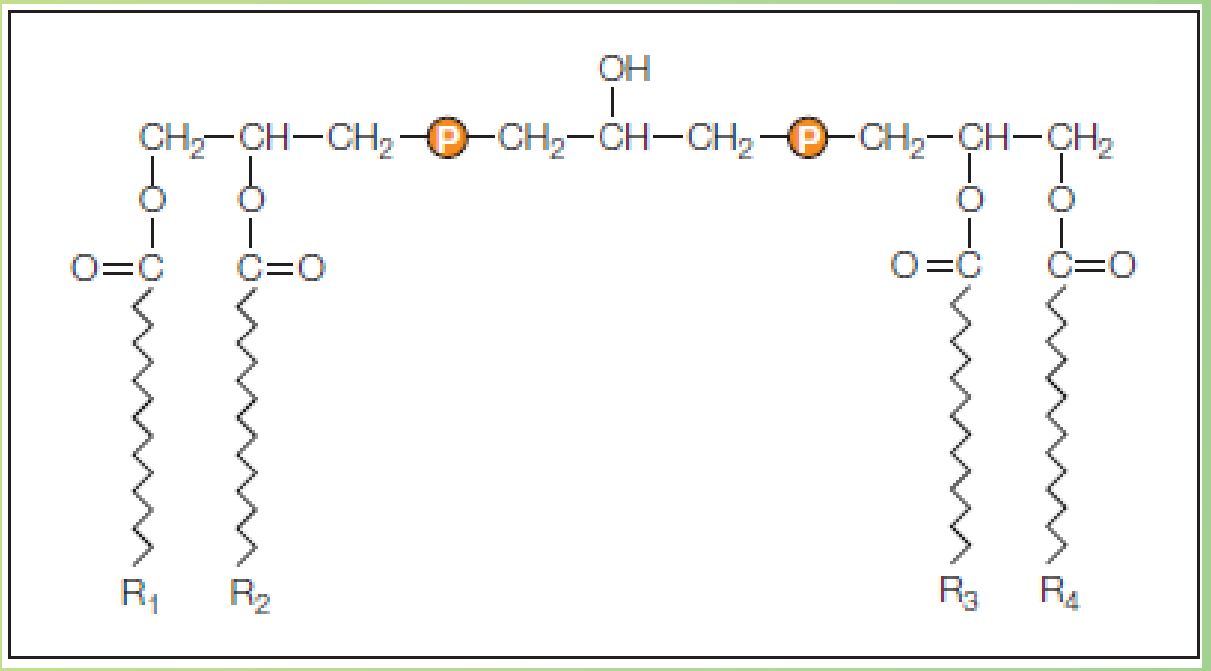
Mitochondrial phospholipids Phosphatidyl…

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



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.



Mitochondrial diseases

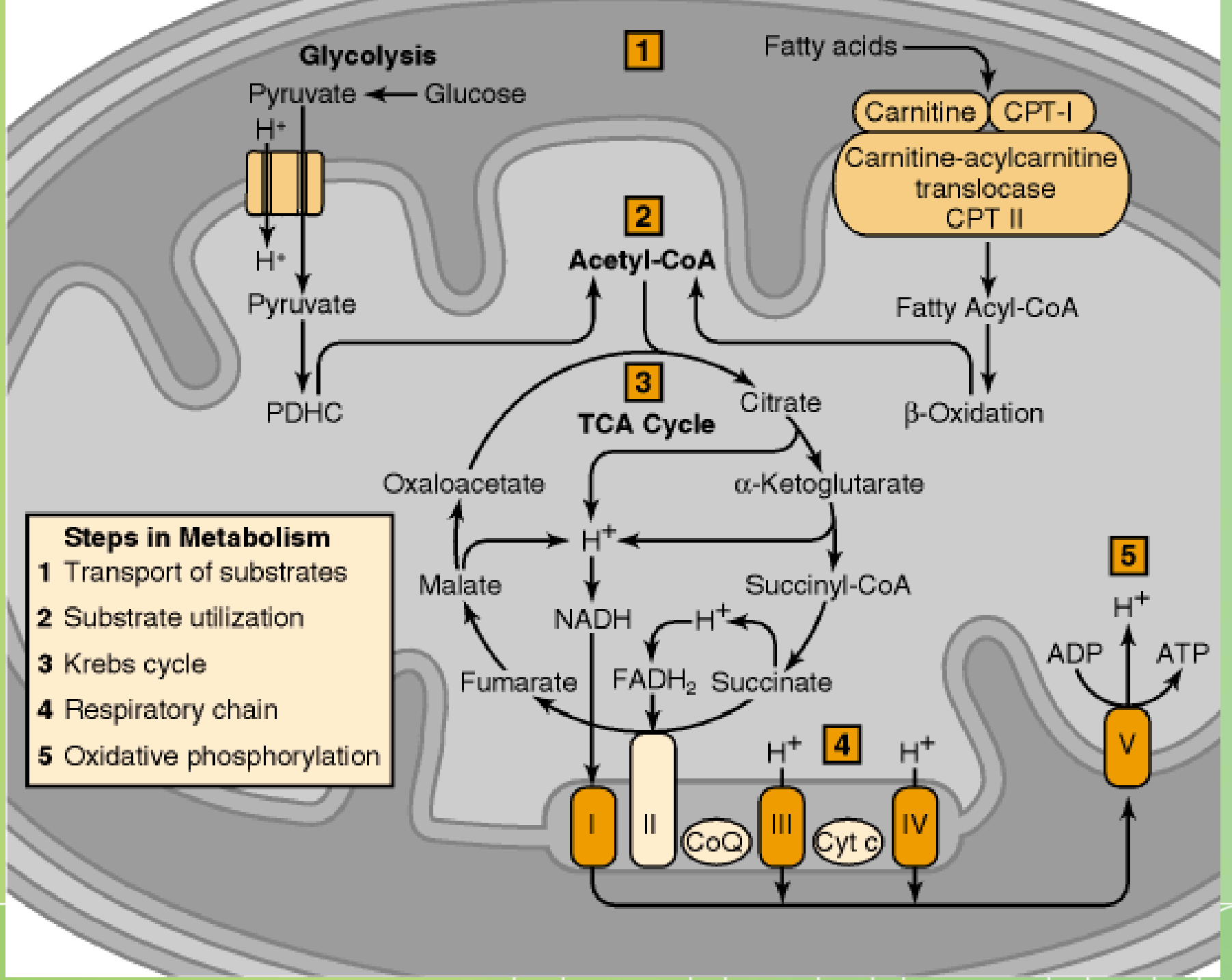
General information

- The mammalian oocyte contains around 10^5-10^8 mitochondria and each one contains 2-10 copies of mitochondrial DNA, which are mainly inherited from the mother.
- If the mitochondrial genomes carry 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

Mitochondria diseases can be classified according to their cause: genetic or biochemical.

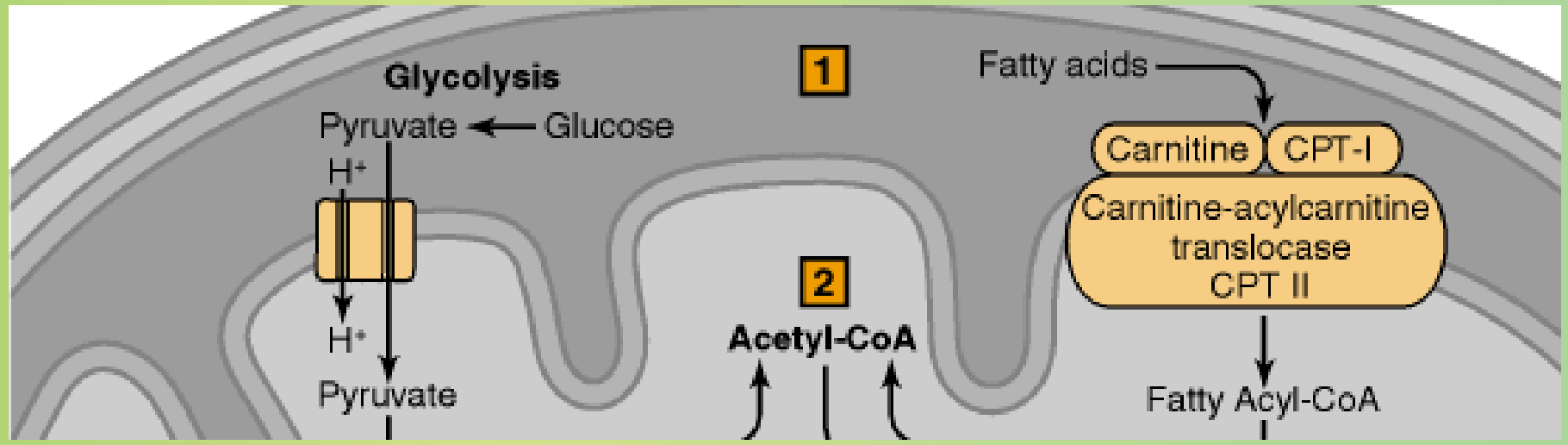
The biochemical classification of mitochondrial diseases

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


Glycolysis
1
Fatty acids
Pyruvate
Glucose
Carnitine
CPT-I
Carnitine-acylcarnitine translocase
CPT II
H+
2
Acetyl-CoA
H+
Pyruvate
Fatty Acyl-CoA
PDHC
3
TCA Cycle
Citrate
β-Oxidation
Oxaloacetate
α-Ketoglutarate
Steps in Metabolism
1 Transport of substrates
2 Substrate utilization
3 Krebs cycle
4 Respiratory chain
5 Oxidative phosphorylation
H+
5
Malate
NADH
H+
Succinyl-CoA
H+
ADP
ATP
Fumarate
FADH2
Succinate
V
H+
4
H+
I
II
CoQ
III
Cyt c
IV

Defects of mitochondrial transport

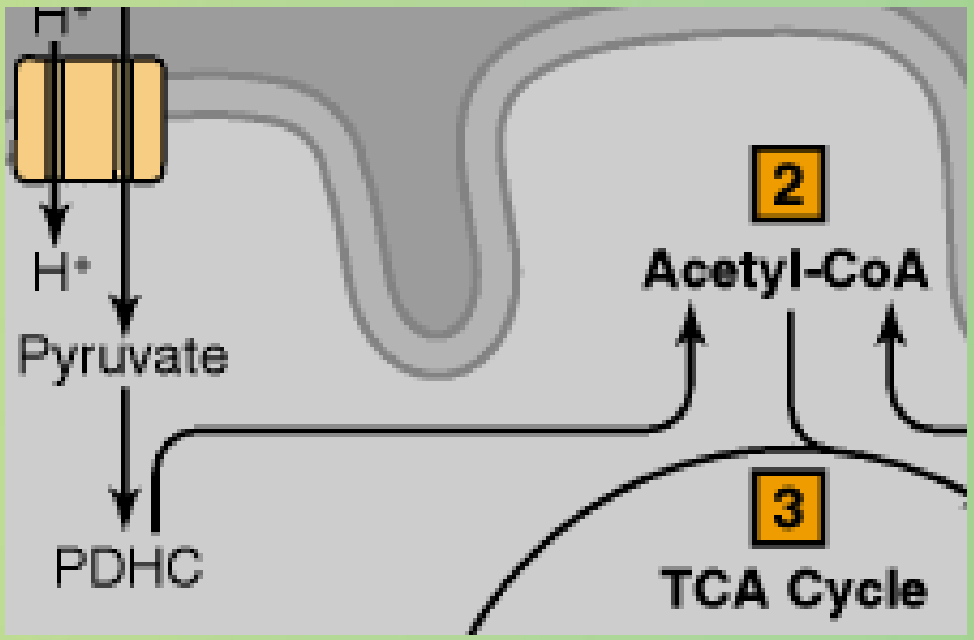
- interfere with the movement of molecules across the inner mitochondrial membrane, which is tightly regulated by specific translocation systems.



Substrate utilization

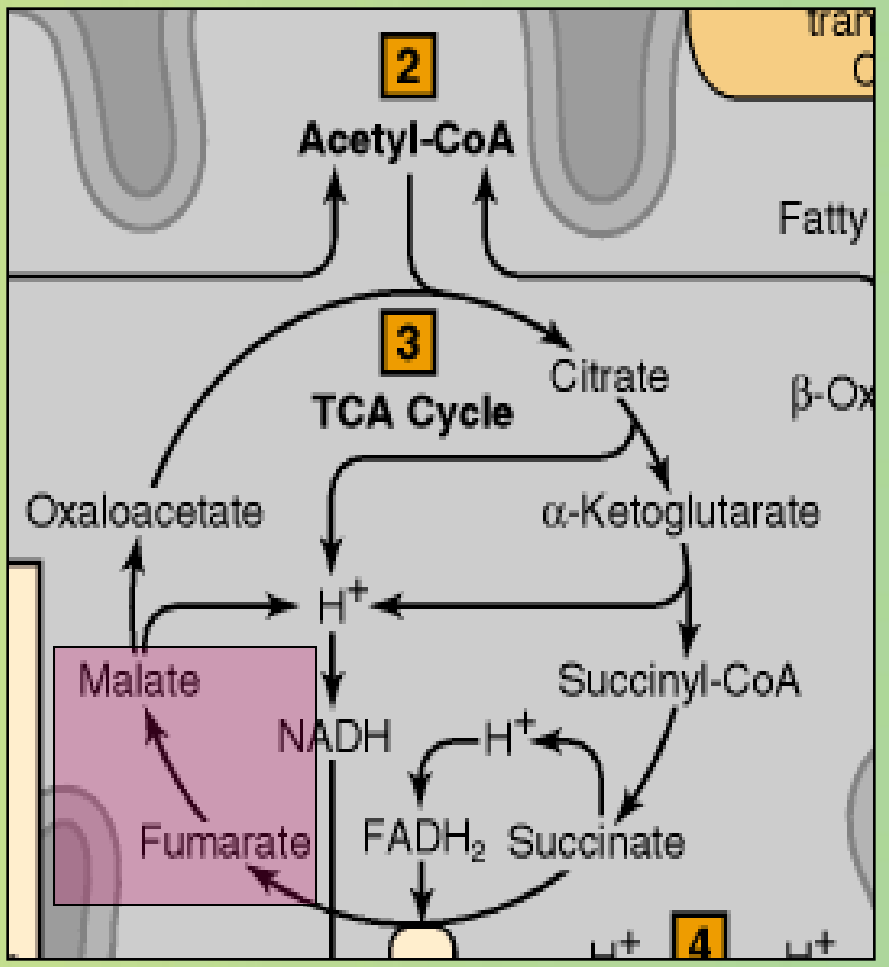
- Pyruvate dehydrogenase (PDH) deficiency can cause alterations of pyruvate metabolism.
- The PDH complex (PDHC) catalyzes the irreversible conversion of pyruvate to acetyl-CoA.

- **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 blood or CSF, and associated elevations of pyruvate and alanine.**



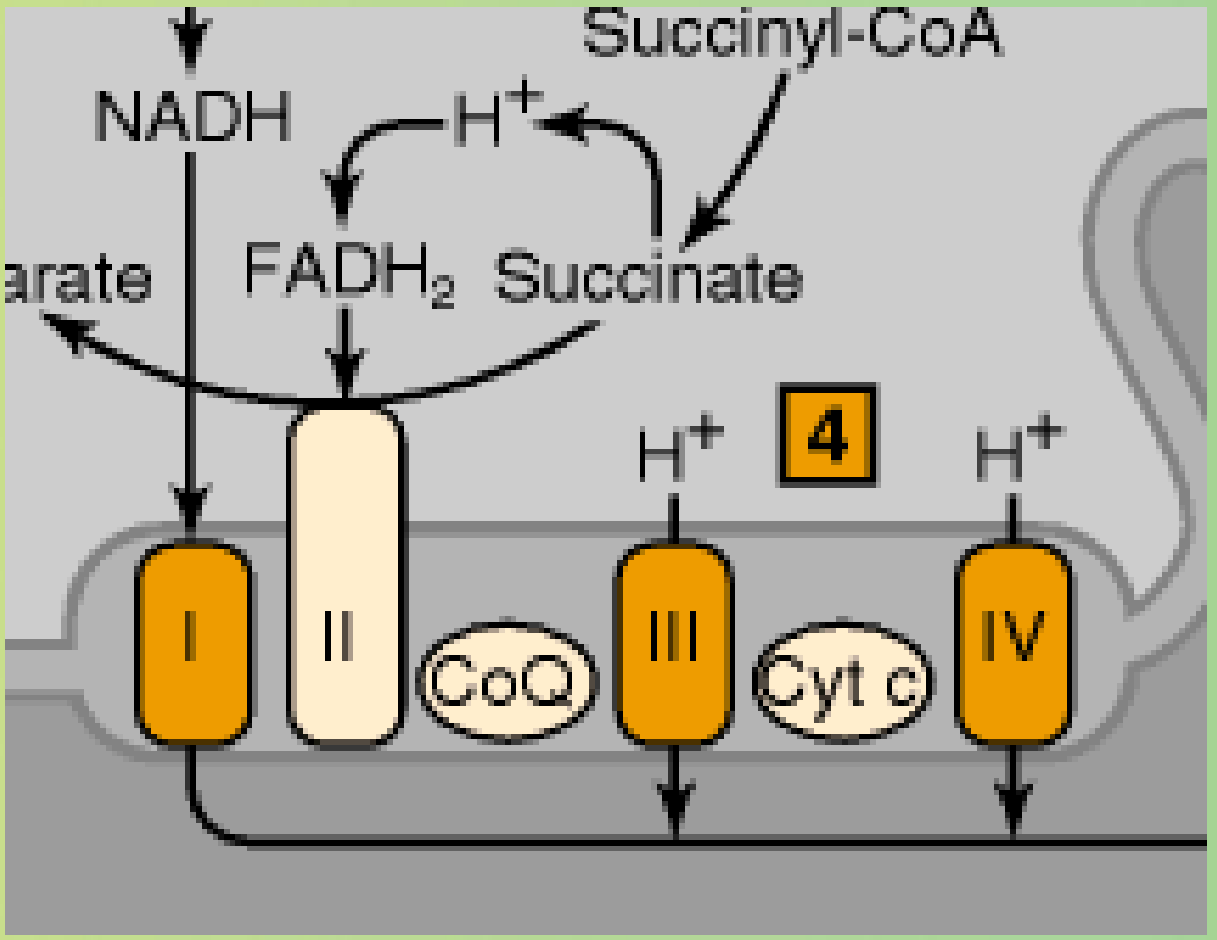
Defects of the Krebs cycle

- Fumarase deficiency is reported in patients having mitochondrial encephalomyopathy.
- Features: excretion of large amounts of fumarate and, to a lesser extent, succinate in the urine.



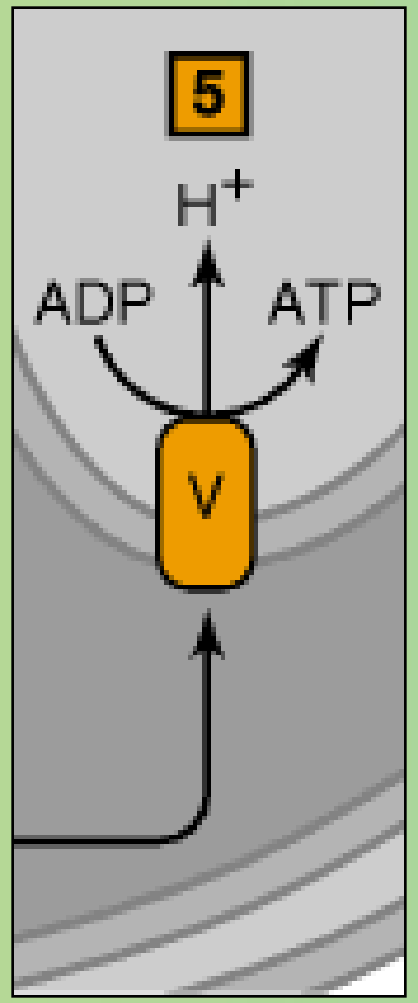
Abnormalities of the respiratory chain reaction

- Defect in any of the 4 electron chain complexes have been reported.



Defects of oxidation-phosphorylation coupling

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



The genetic classification of mitochondrial diseases

Defects of mitochondrial DNA (mtDNA)

- These disorders are associated with dysfunction of the respiratory chain because all 13 subunits encoded by mtDNA are subunits of respiratory chain complexes.
- Diseases due to point mutations are transmitted by maternal inheritance.

MERRF and others

- One main syndrome is myoclonic epilepsy and ragged red fiber disease (MERRF), which can be caused by a mutation in one of the mitochondrial transfer RNA genes required for the synthesis of the mitochondrial proteins responsible for electron transport and production of ATP.
- Other syndromes include
  - Lactic acidosis and stroke-like episodes (MELAS)
  - Leber's hereditary optic neuropathy (LHON),
  - Neurogenic atrophy, ataxia and retinitis pigmentosa (NARP)

Leber's hereditary optic neuropathy (LHON)

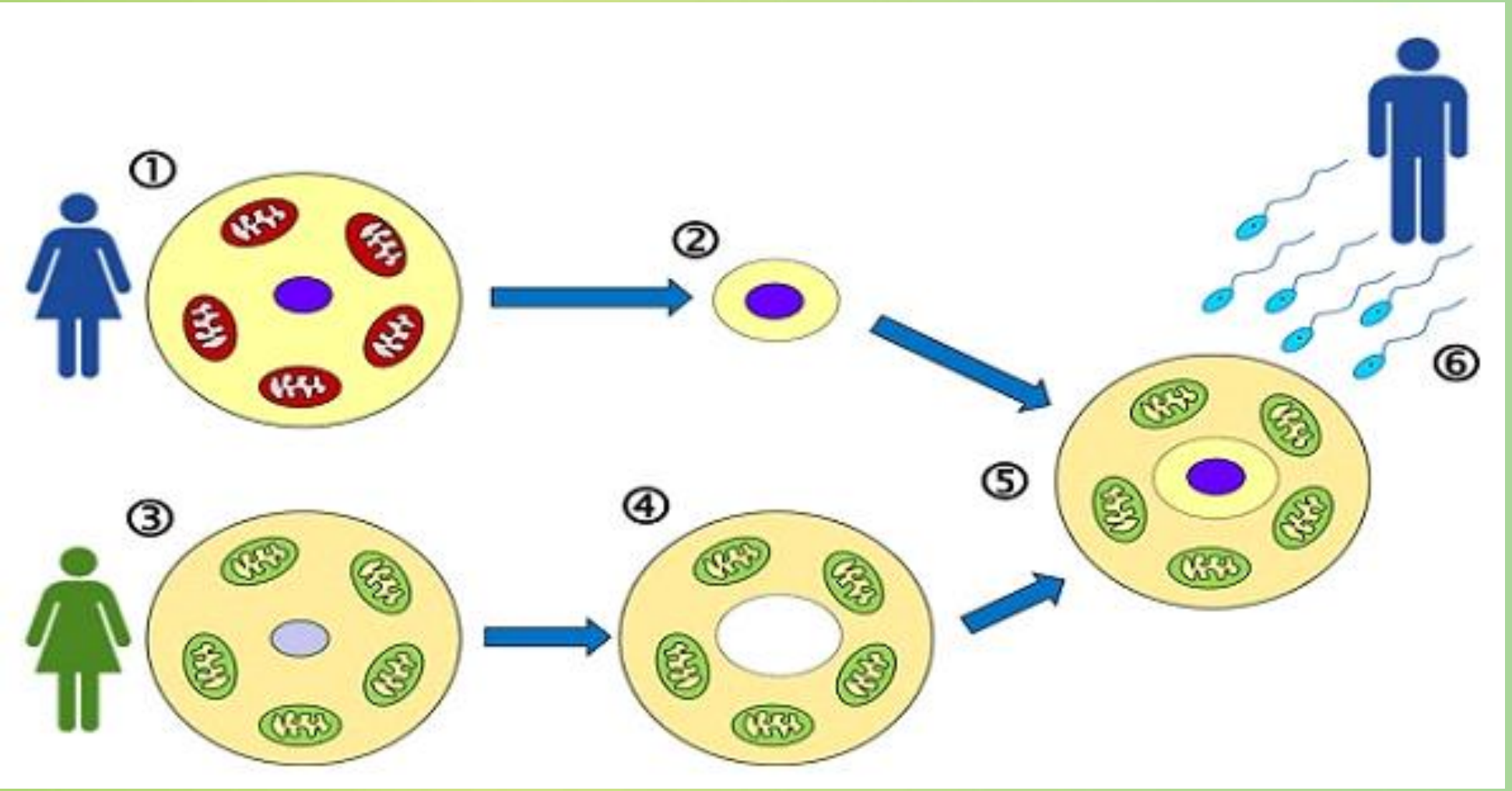
- Females (10%) are affected less frequently than males (50%), but males never transmit LHON to their offspring and not all individuals with mutations develop the disease.
  - Inheritance is mitochondrial (cytoplasmic) not nuclear.
- The mutations reduce the efficiency of oxidative phosphorylation and ATP generation.

- **A rare inherited disease that results in blindness because of degeneration of the optic nerve.**
- **Vision loss is only manifestation, occurs between 15-35.**

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



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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

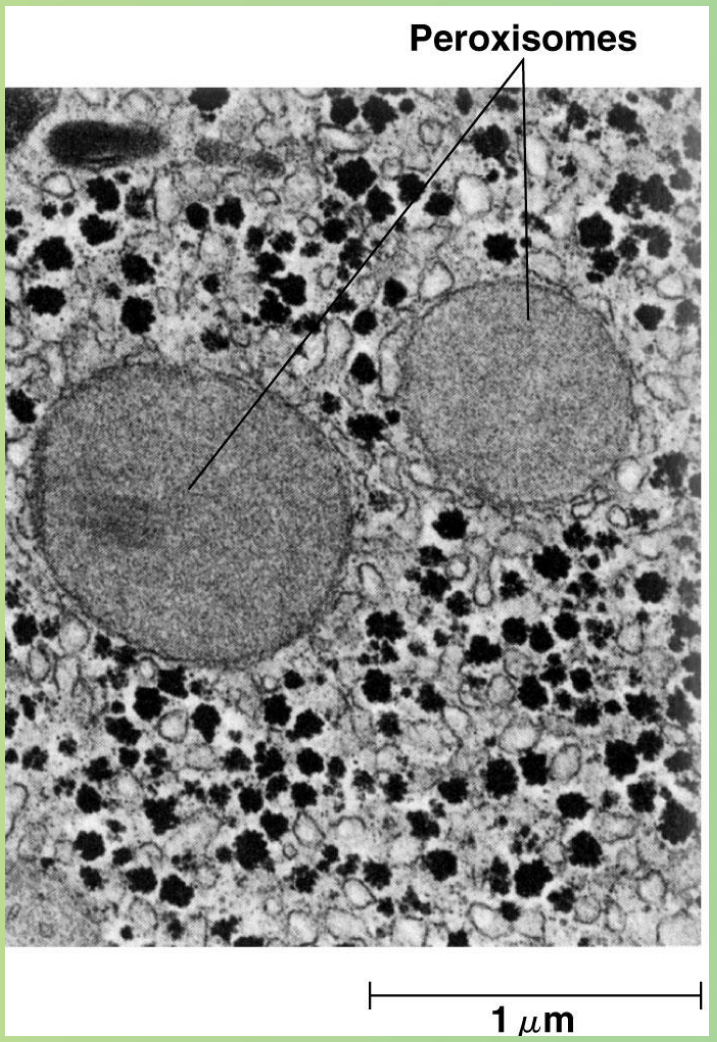
The Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques, although the procedure is illegal in most countries

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.

Peroxisomes

Structural features of peroxisomes

- Small, membrane-enclosed organelles
- They contain enzymes involved in a variety of metabolic reactions, including energy metabolism.
- They replicate by division.
- Most human cells contain 500 peroxisomes.

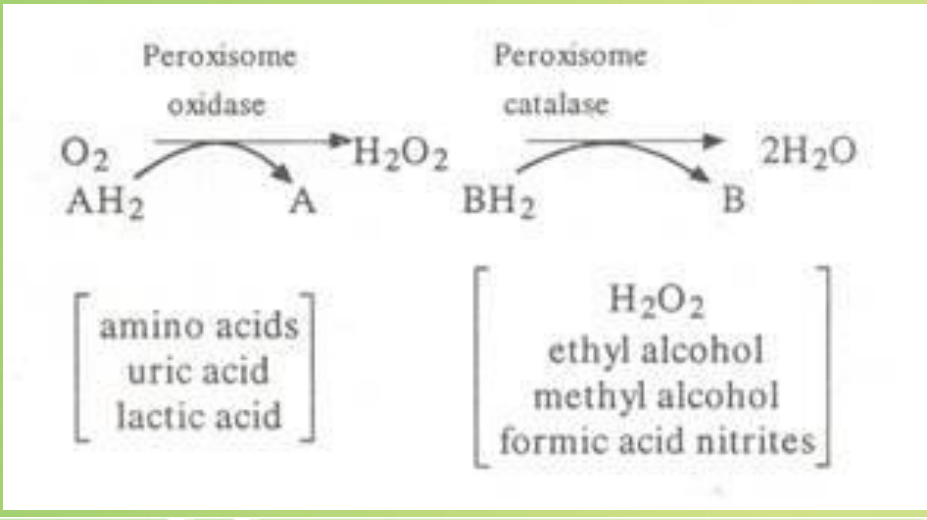


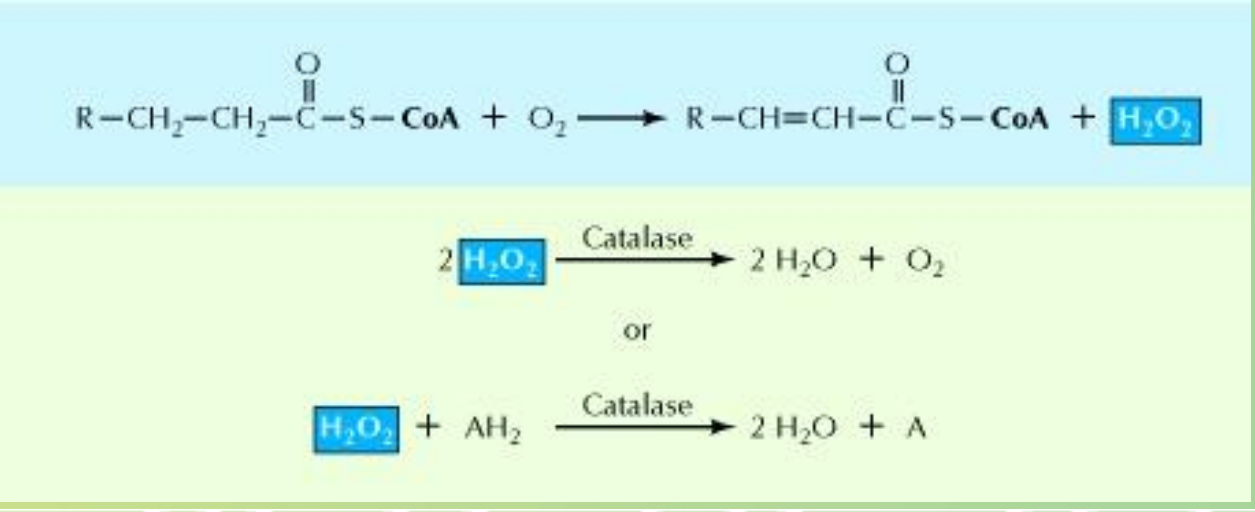
Peroxins

- Peroxisomal proteins are called peroxins.
- There are 85 genes that encode peroxins, most of which are metabolic enzymes.
- Internal proteins are synthesized on free ribosomes and then imported into peroxisomes.
- Other membrane proteins act as receptors for the import of internal proteins.

Function of peroxisomes

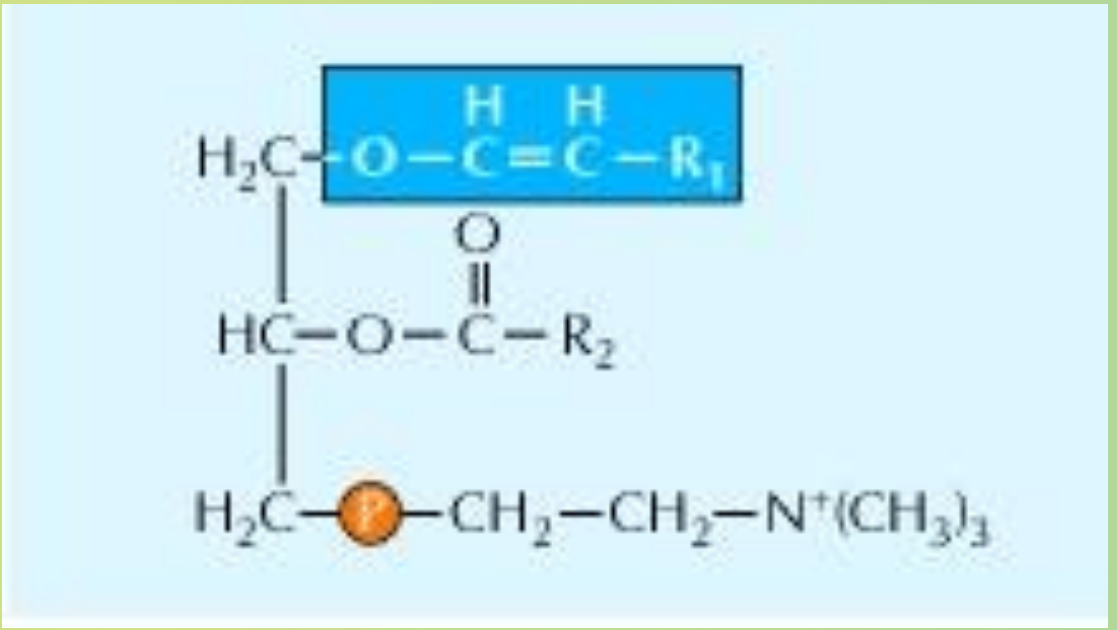
- Peroxisomes carry out oxidation reactions producing hydrogen peroxide, which is harmful to the cell
- But peroxisomes contain the enzyme catalase that concerts it to water and oxygen
- Substrates like uric acid, amino acids, and fatty acids are broken down by oxidative reactions in peroxisomes.
  - Fatty acids are oxidized in both peroxisomes and mitochondria.





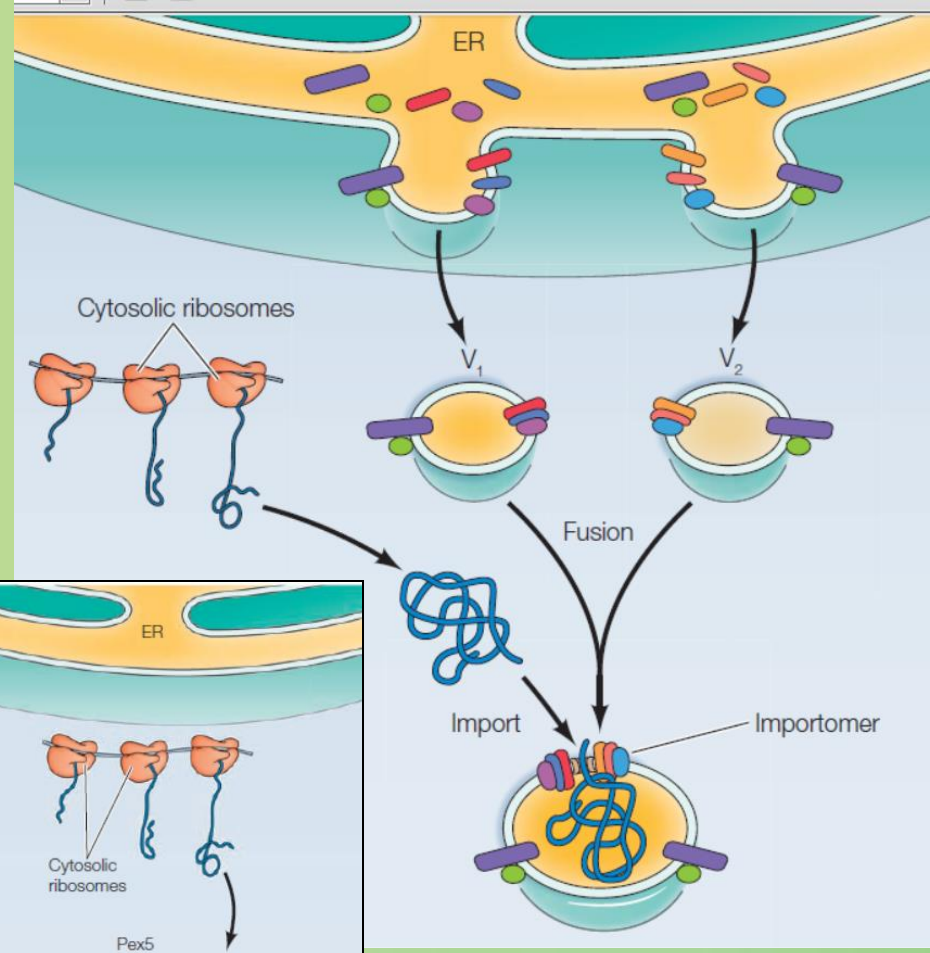
Synthesis in peroxisomes

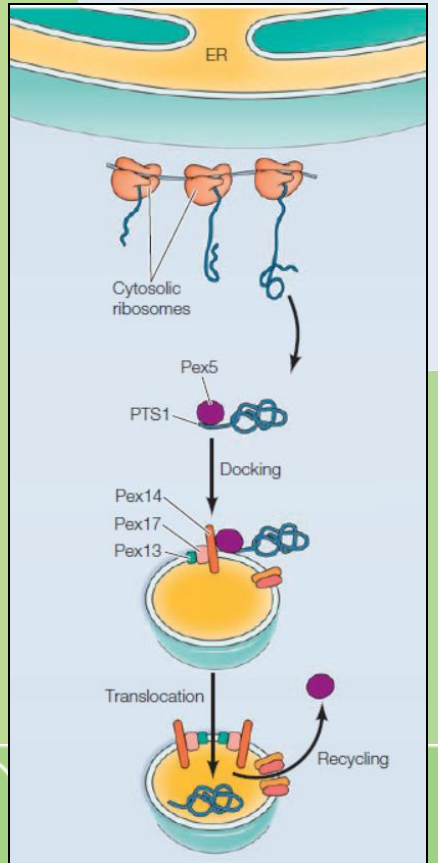
- Cholesterol
- Bile acids (liver)
- Plasmalogens
  - important in membranes of the heart and brain



Assembly of peroxisomes

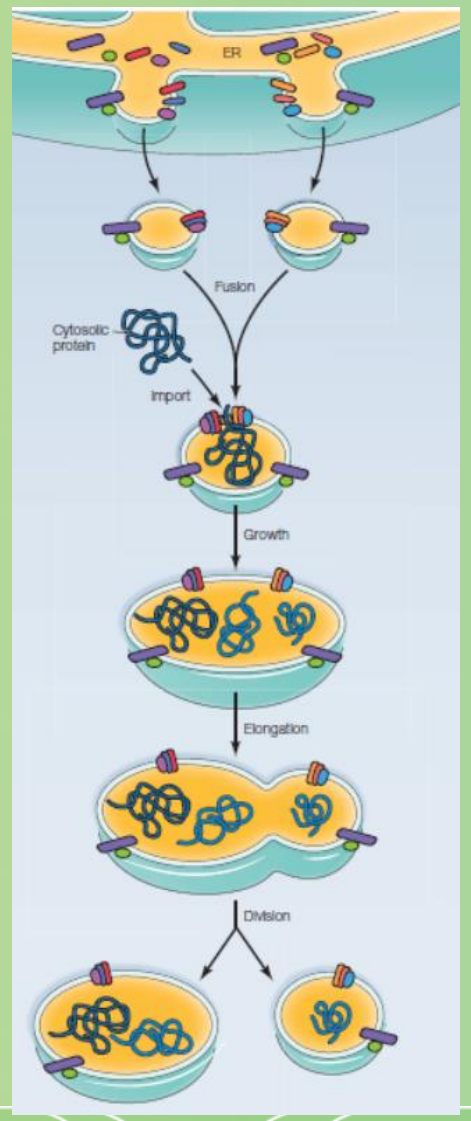
- Peroxisomal transmembrane proteins are derived from the ER.
- A functional peroxisome is formed from carrying distinct transmembrane proteins.
- The internal peroxisomal proteins synthesized on cytosolic ribosomes can then be imported.
- Peroxisomal matrix proteins contain a targeting signal called PTS1.
- Different peroxins help in translocating the peroxisomal proteins into the peroxisomes by functioning in carrying and importing them.





Formation of new peroxisomes

- New peroxisomes can be formed de novo by two mechanisms:
  - The fusion of vesicles budding from the ER followed by the import of cytosolic proteins.
  - New peroxisomes can be formed by the growth and division of old ones.



Peroxisomal diseases

- Single peroxisomal enzyme deficiencies
  - Defective specific peroxisomal enzymes
- Peroxisomal biogenesis disorders (PBDs).
  - Mutations of PEX genes leading to deficiencies of multiple peroxisomal enzymes
  - Example: Zellweger syndrome
    - Lethal
    - Due to mutations in at least 10 genes
- X-linked adrenoleukodystrophy (XALD).
  - Defective transport of very long-chain fatty acid (VLCFA) across the peroxisomal membrane.