Mitochondria

Granular or filamentous organelles of cytoplasm. They are regarded as ***biochemical machines*** that convert the potential energy of food stuff to kinetic energy.

Mitochondria (Historical background)

- First isolated from the cells of insect striated muscle by ***Kolliker*** around ***1850.***
- ***Altman*** described them as "bioplasts" in ***1890.***
- ***Benda*** in ***1897*** introduced the term "mitochondria".
- Mitochondrion-singular
- Mitochondria-plural

Mitochondria (Distribution)

- Present in eukaryotic cells and absent in prokaryotic cells.
- Generally remain **uniformly scattered** throughout the cytoplasm of the cell but they may orient themselves around the nucleus or the peripheral cytoplasm.
- Mostly localised to those particular site which are engaged in metabolic activities.
- During cell division mitochondria gather near the spindle and form rings around the myofibrillar bands in the **muscle cells**.
- In the **neurons** they occur in the region of nerve impulse transfer.

Number: varies from few thousand to few lakhs depending on the organ or species.

Size: Variable. Width almost same and measuring from 1-4µm.

Shape: Mitochondria are sausage shaped but they may be also granular, rod shaped, filamentous, spherical or thread like. During functional stages they may assume other shapes like club shaped, vesicular. In many electronmicrograph they appear to be dumbbell shaped or rocket shaped.

Structure: Under E.M a mitochondrion appears as a double walled structure like an ice box. It consists of an outer and inner membrane and enclose within them two compartments or chambers.

I. Mitochondrial membrane

Both the mitochondrial membranes are trilaminate having a biomolecular lipid core and extrinsic and intrinsic proteins. Membranes are about 60-80 A^{o} thick.

A. **Outer mitochondrial membrane**:

- It forms uninterrupted outer boundary of mitochondria.
- It isolates the mitochondrial content from the cytosol.
- It is freely permeable to various soluble metabolites entering into the mitochondrial matrix from the cytosol.

- **Porin** is present on the outer membrane and provides channels for passage of molecules of less than 5000D including metabolites required for ATP synthesis.

B. Inner Mitochondrial membrane:

- The inner membrane is projected into the central space in the form of finger like projections or inpushings. These are known as ***cristae or mitochondrial crests*****.**
- These are usually in the form of incomplete septa and divide the matrix into interconnected chambers.
- The outer face of the inner membrane is called **C face or cytosol face** which is directed towards the outer chamber. The inner face is known as **m-face or matrix face** which is directed towards the matrix.
- The number of cristae vary in number and shape depending on the species, tissue and metabolic state.
- Four complexes (I to IV) of integral membrane protein are present on the inner membrane. These proteins use the transport of energetic electrons to create a proton gradient across the inner membrane.
- Contacts between the inner and outer membranes are sites of protein import.

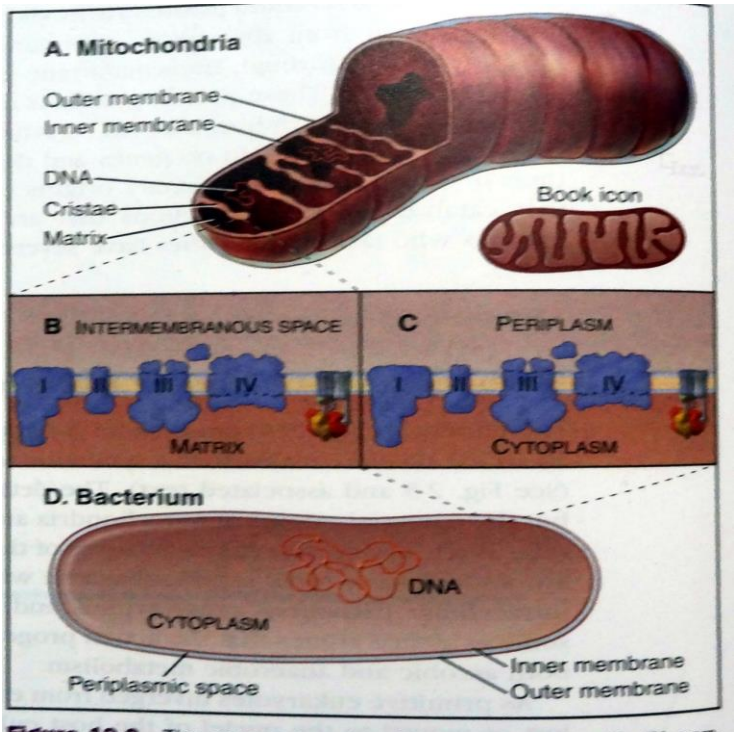


Figure 19-2 The compartments of a mitochondrion **(A–B)** compared with a Bacterium **(C–D).** Respiratory chain complexes I to IV are labeled with roman numerals.

Mitochondrial chamber

1. **Outer Chamber**:

- It is the space between the outer membrane and inner membrane of mitochondria which also extends into the core of cristae.
- It is about 60-80^{o}A in width and is filled with a fluid of low viscosity and low density containing some enzymes but is generally devoid of inclusions.

2. **Inner chamber:**

- It is the space enclosed by the inner membrane. It is a wide space and is filled with mitochondrial matrix.
- The matrix is gel like and contains a number of enzymes of the Kreb's cycle, some lipids, circular DNA molecule and 70S ribosome.
- Fine granules- the binding site for bivalent cations are also present within the mitochondrial matrix.

Mitochondrial Crest or cristae

The shape and arrangements are variable. The arrangements of crest may be of following type:-

- **Parallel**: to the long axis of mitochondria as in the neurons.
- **Perpendicular:** to the long axis of mitochondria as in most animal cells.
- **Haphazardly**: Distributed i.e project into the matrix from all sides as in protozoa and many plant cells.

Mitochondria(Elementary particles):

- The inner membrane and cristae are seen to be covered with special particles known as **elementary particles** which was first reported by H.F Moran in 1962.
- Each elementary particle is differentiated into a base piece, a stalk and a head piece.
- The head piece is known as **F_1 particle** while the stalk and the base piece is known as **F_0 particle**.
- The head piece and tail piece are more or less similar in diameter which is about 75-100^{o}A and the stalk has a length of about 50 ^{o}A.
- These particles possess coupling factors and ATP synthase enzyme.
- No. varies from 10^4- 10^5 .

Mitochondrial enzyme system:

- In a mitochondrion more than 70 enzymes and coenzymes work in an orderly fashion.
- There are many cofactors and metals required for the enzymatic activity as well as mitochondrial function.

A. **Enzyme of Kreb's Cycle:**

B. **Enzymes of ETS.**

Mitochondrial DNA:

- A mitochondrion may contain 1-more DNA molecules depending upon its size.
- It appears as a circular, highly twisted double stranded molecule.
- It can replicate and divide into several circles which may be found even in the single mitochondrion.
- These mitochondrial genomes encode RNA and proteins that are essential for mitochondrial function including ATP synthesis.
- Human mitochondrial genome is 16569bp long and encodes only 13 mitochondrial membrane protein, 2 rRNAs and 22 tRNAs.
- Other mitochondrial proteins are encoded by nuclear DNAs.
- All mitochondrial proteins that are encoded by nuclear genes are synthesized in the cytoplasm and subsequently imported in the mitochondria.

Mitochondrial DNA vs. nuclear DNA:

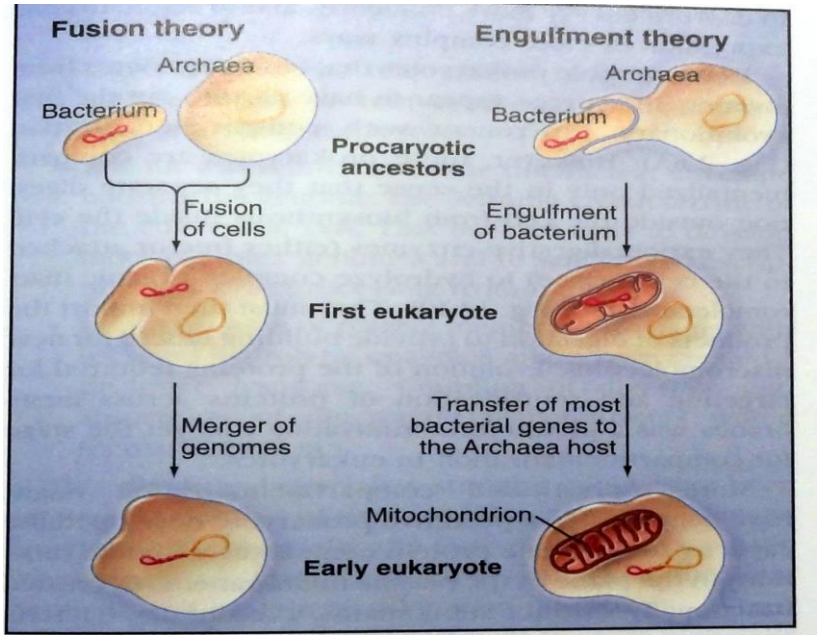
1. Circular in shape.
2. Higher GC content and higher buoyant density
3. Higher melting point.
4. Rate of renaturation higher.
5. Transcription symmetric i.e both strands of same genetic locus are transcribed.
6. Replication time between G_2 phase and cytokinesis.

MICOS:

- A complex of five transmembrane proteins and two soluble proteins stabilizes the junction of cristae with the inner membrane. The complex is called MICOS for **mitochondrial contact site and cristae organizing system**, because loss of these proteins results in disorganized cristae.
- MICOS links the inner and outer membranes and separates the transmembrane proteins of the inner membrane into two domains.

Origin and evolution of Mitochondria

Eukaryotes have acquired mitochondria when an α protobacterium became an **endosymbiont.**



Origin and evolution of Mitochondria:

- The mitochondrial progenitor brought along its own genome and biosynthetic machinery, but over many years of evolution, most bacterial genes either moved to the host cell or were lost.
- Like their bacterial ancestors, mitochondria are enclosed by two membranes with the inner membrane equipped for ATP synthesis.
- Mitochondria maintain a few genes for mitochondrial components and the capacity to synthesize protein.
- Even though acquisition of mitochondria might have been the **earliest event in eukaryotic evolution,** some eukaryotes lack fully functional mitochondria.

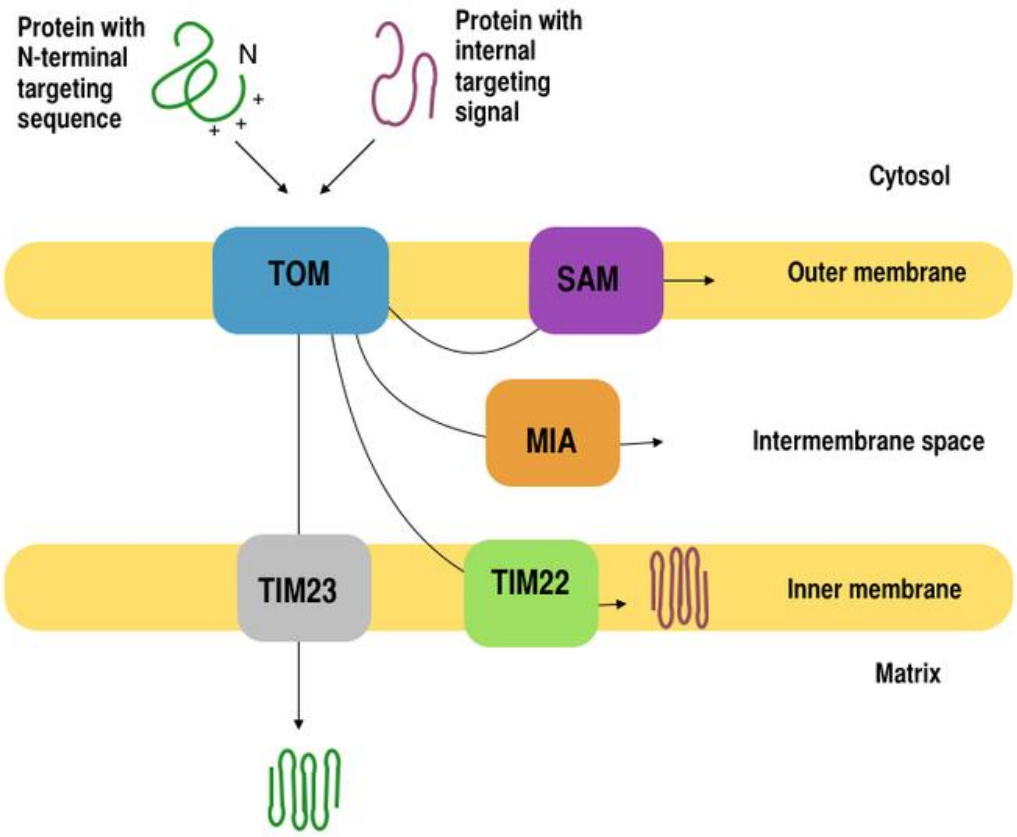
Biogenesis of Mitochondria:

- The ability for a mitochondrion to self-replicate is called biogenesis.
- The mitochondrion is a key regulator of the metabolic activity of the cell, and is also an important organelle in both production and degradation of free radicals. It is reckoned that higher mitochondrial copy number (or higher mitochondrial mass) is protective for the cell.
- Mitochondria are produced from the transcription and translation of genes both in the nuclear genome and in the mitochondrial genome.
- The majority of mitochondrial protein comes from the nuclear genome, while the mitochondrial genome encodes parts of the electron transport chain along with mitochondrial rRNA and tRNA.
- Mitochondrial biogenesis increases metabolic enzymes for glycolysis, oxidative phosphorylation and ultimately a greater mitochondrial metabolic capacity.

- However, depending on the energy substrates available and the REDOX state of the cell, the cell may increase or decrease the number and size of mitochondria.
- Critically, mitochondrial numbers and morphology vary according to cell type and context-specific demand, whereby the balance between mitochondrial fusion/fission regulates mitochondrial distribution, morphology, and function.
- Mitochondria grow by importing most of their proteins from the cytoplasm and replication of the genome. Targetting and sorting signals built into the mitochondrial proteins that are synthesized in the cytoplasm direct them to their destinations.
- Like the cells mitochondria may divide.
- Unlike cells, they may also fuse with other mitochondria. Balance between a fusion and division determines the number of mitochondria in a cell.

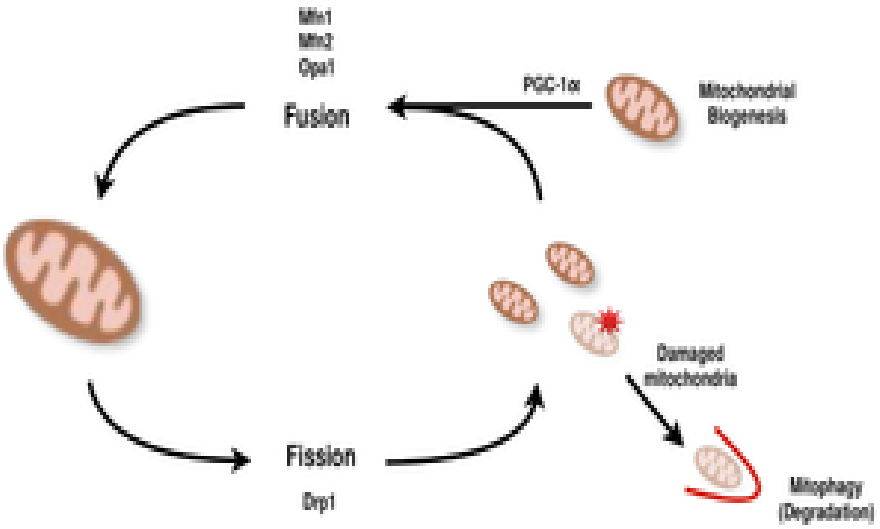
Protein import:

- Since the majority of mitochondrial protein comes from the nuclear genome, the proteins need to be properly targeted and transported into the mitochondria to perform their functions
- First, mRNA is translated in the cell's cytosol. The resulting unfolded precursor proteins will then be able to reach their respective mitochondrial compartments.
- Precursor proteins will be transported to one of four areas of the mitochondria, which include the outer membrane, inner membrane, intermembrane space, and matrix. All proteins will enter the mitochondria by a translocase on the outer mitochondrial membrane (TOM).
- During the past two decades, researchers have discovered over thirty proteins that participate in mitochondrial protein import.



Fusion and fission

- Mitochondria are highly versatile and are able to change their shape through fission and fusion event.
- fission is the event of a single entity breaking apart, whereas fusion is the event of two or more entities joining to form a whole. The processes of fission and fusion oppose each other and allow the mitochondrial network to constantly remodel itself.
- If a stimulus induces a change in the balance of fission and fusion in a cell, it could significantly alter the mitochondrial network.
- For example, an increase in mitochondrial fission would create many fragmented mitochondria, which has been shown to be useful for eliminating damaged mitochondria and for creating smaller mitochondria for efficient transporting to energy-demanding areas. Therefore, achieving a balance between these mechanisms allow a cell to have the proper organization of its mitochondrial network during biogenesis and may have an important role in muscle adaptation to physiological stress.



The processes of fusion and fission allow for mitochondrial reorganization.

- Fusion and division depends on proteins with GTPase domains related to dynamin and its gene has been acquired by eukaryotes from the bacterium that became mitochondria.
- For division: one dynamin related GTPase is required and this is self assembled into spirals that appear to pinch mitochondria into two. The process of mitochondrial fission is directed by Drp1, a member of the cytosolic dynamin family. During apoptosis, this GTPase also participates in fragmentation of mitochondria.
- **For fusion:** two GTPases are required, one anchored in the outer membrane and other in the inner membrane both linked by **adapter protein** in the intermembrane space. Fusion at the level of the outer mitochondrial membrane is mediated by Mfn1 and Mfn2 (Mitofusins 1 and 2 and fusion at the level of the inner mitochondrial membrane is mediated by Opa1.
- Fusion of the outer membrane requires a proton gradient across the inner membrane, while fusion in the inner membrane depends on the electrical potential across the inner membrane.

Loss of function or mutation in fusion protein lead to cells with numerous small mitochondria and some lacking even mt DNA.

Human mutation in the genes for fusion proteins result in defects in the myelin sheath that insulates axon (one form of Charcot Marie tooth disease) and the atrophy of the optic nerve.

Mitochondria and diseases:

- Mitochondrial dysfunction contributes to a remarkable diversity of human diseases including ***seizures, strokes, optic atrophy, neuropathy, myopathy, cardiomyopathy, hearing loss and Type 2 diabetes mellitus.***
- Mutations in nuclear genes for mitochondrial proteins cause similar diseases.

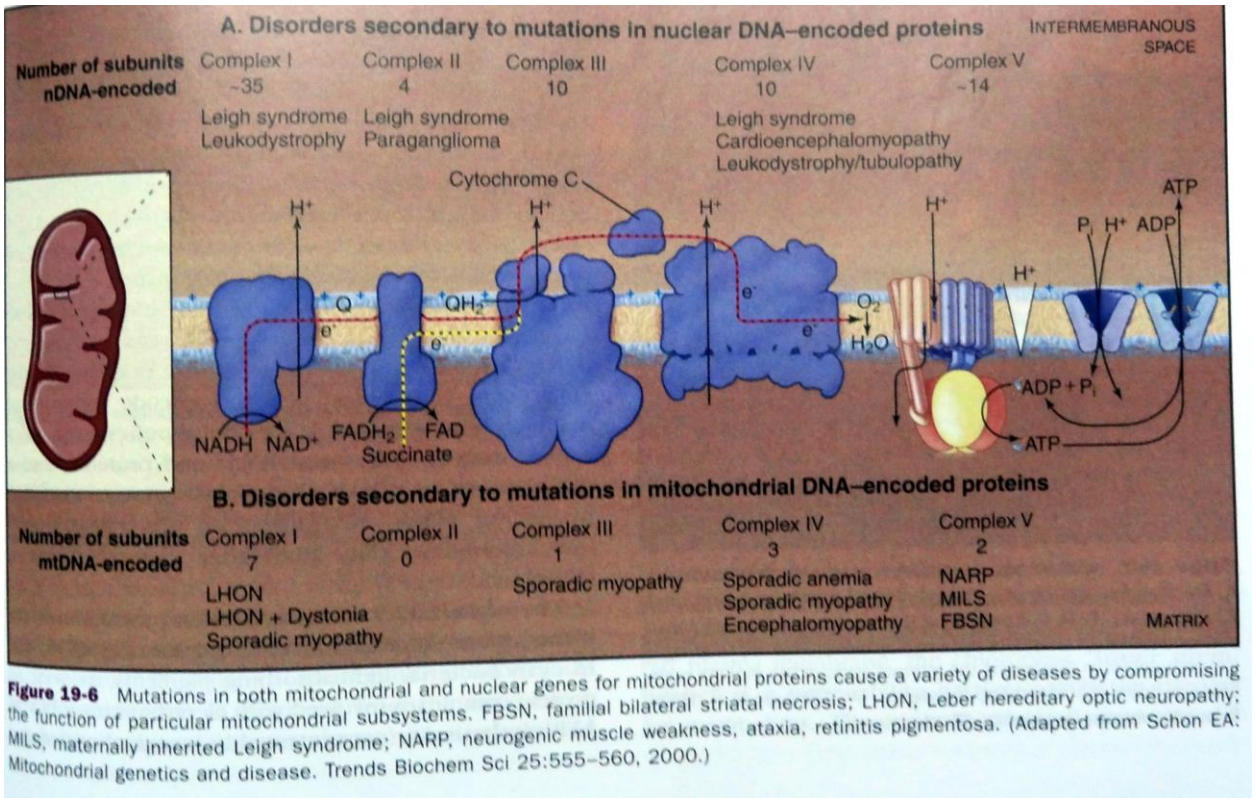


Figure 19-6 Mutations in both mitochondrial and nuclear genes for mitochondrial proteins cause a variety of diseases by compromising the function of particular mitochondrial subsystems. FBSN, familial bilateral striatal necrosis; LHON, Leber hereditary optic neuropathy; MILS, maternally inherited Leigh syndrome; NARP, neurogenic muscle weakness, ataxia, retinitis pigmentosa. (Adapted from Schon EA: Mitochondrial genetics and disease. Trends Biochem Sci 25:555–560, 2000.)