

# A Review in Mitochondria and Some of its Diseases

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**Abstract:** A cell is said to be a “unit of life” since its function, make the organisms to stay alive. Cellular functions are regulated and performed by various cell organelles. One such important cell organelle is mitochondria, which is said to be “power house of the cell”, because mitochondria generate energy for cellular metabolism. Mitochondria, generates energy by various biochemical reactions which result in the synthesis of energy in the form of ATP (adenosine tri-phosphate). Many different enzymes, co-factors, substrate involves in the ATP synthesis are encoded by mitochondrial DNA (mtDNA). When these mtDNA gets mutated, it leads to mitochondrial diseases. Mitochondrial diseases cause biochemical malfunction of a cell. Since mitochondria are inherited from mother to offspring, mitochondrial diseases also get inherited from a carrier mother. This condition is known as maternal inheritance during fertilization. These mitochondrial diseases has no cure but can be diagnosed by prenatal screening as well as by comparing mtDNA sequence of a patient with Cambridge reference sample of mtDNA, which is the first mtDNA sequence analysed in Europe. This comparison pays way for phylogenetic analysis. Mitochondrial diseases result in mortality.

**Keywords:** mtDNA, ATP synthesis, maternal inheritance

## 1. Introduction

Mitochondrion is one of the cell organelle which is known as “power house of the cell”. Its main function is to generate energy from food and supply it in the form of ATP to the cells for its cellular metabolism. The reaction involved is known as cellular respiration. According to “endosymbiotic theory” it has been stated that “mitochondria and chloroplast which has now seems to be cell organelle, are related to Richett’s probacteria and cyanobacteria respectively. Through binary fission, genetic material of these bacteria is engulfed by Eukaryotes, which has been changed into cell organelle of eukaryotes because of evolutionary changes through binary fission.

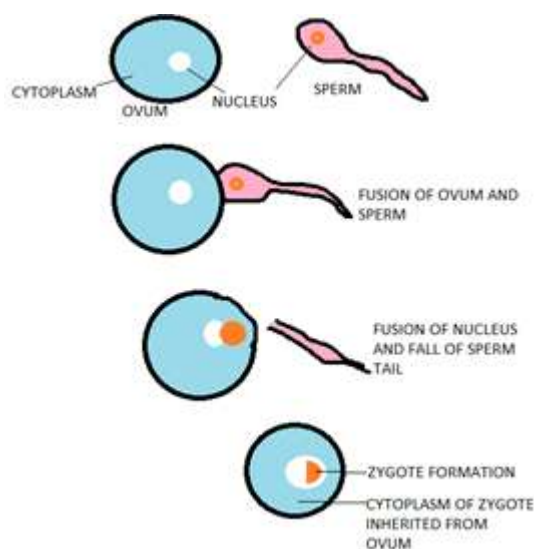
Mitochondria get inherited from egg cells of a mother to offspring called “maternal inheritance”. Wherein, mitochondria of a sperm cell are present in the tail of the sperm, which gets disrupted during fertilization. Since only nucleus of the sperm cell can enters into ovum. Any mutational changes in the maternal mitochondrial DNA get inherited to the offspring which gets affected by mitochondrial disease.

Let us discuss in detail about mitochondria and its related diseases in this review article.

## 2. Maternal Inheritance

During fertilization, one sperm from male which is the smallest cell and one ovum from female which is the largest cell fuse together and fertilize forms zygote. Zygote contains 46 chromosomes (i.e.) 23 chromosomes from sperm and 23 chromosomes from ovum are contributed. Thus, the nucleic acid of a zygote is shared by both father and mother. Wherein, other cell organelles including cytoplasm are provided by mother to the zygote.

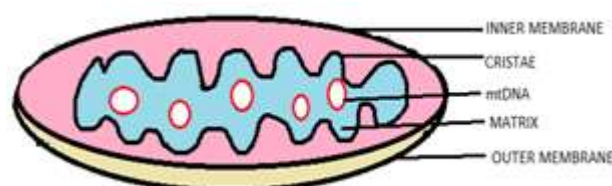
If mother seems to be a carrier of mitochondrial diseases, it will be inherited to zygote. Thus, mitochondrial diseases are most common in female than male. This is known as maternal inheritance.



## 3. Structure of Mitochondria

Mitochondrion is a spherical shaped cell organelle consists of outer membrane, inner membrane, cristae and matrix.

- **Outer membrane:** It is made up of porins which protects and provides structure to the mitochondria. It regulates the flow of hydrophobic proteins in and out of the mitochondria.
- **Inner membrane:** It is made up of cardiolipin. It is a region where biochemical reactions take place.
- **Cristae:** It is folded in structure. There are numerous folds which have been folded inwards.
- **Matrix:** matrix is a region found inside the cristae. It consists of mitochondrial DNA (mtDNA), which codes for proteins, which involves in ATP synthesis. Each mitochondrion has nearly 10,000 MtDNA in its matrix region. Wherein, mitochondrion of egg cells contains 2, 00,000MtDNA.



#### 4. Structure of Mitochondrial DNA (MtDNA):

MtDNA is a circular double stranded DNA in eukaryotes. Whereas in prokaryotes and in some of the eukaryotes like “Cnidaria”, MtDNA is linear in structure. It contains independent telomere which is treated as a major in in-vitro studies due to its special mechanism of replication. It has been found that sequencing mtDNA reveals phylogenetic evidence of evolution of different species. MtDNA has two regions namely: heavy strand and light strand. This has been differentiated based on the presence of guanine and cytosine. The regions with the presence of high content of guanine is known as heavy strand wherein, region with the presence of high content of cytosine is known as light strand.

Mitogenome (mtDNA) is made up of 16,569 nucleotides among which only 3% of genome is non-coding. Among coding genes only 37 genes involves in transcription and translation. The translated enzymes, tRNA, and rRNA involves in ATP synthesis.

#### Mitochondrial Metabolism

Various biochemical metabolisms take place in mitochondria and release energy in the form of ATP



#### Flow Diagram of Krebs’s Cycle



#### 6. Oxidative Phosphorylation

Oxidative phosphorylation is the metabolic process in which nutrients from food are oxidized and release ATP. This is based on redox-reaction, in which both oxidation and reduction reaction as well as addition of phosphate takes place. This is also known as cellular respiration. It is carried out with the help of complex of proteins this is called “electron transport chain and chemiosmosis”.

#### Electron Transport Chain

It is the process of transfer of electrons from electron donor to electron acceptor. This takes place in the inner membrane of mitochondria. In plants it is most commonly seen in thylakoid which is responsible for photosynthesis. In

(adenosine tri phosphate). These ATP’s are produced by involving in biochemical reactions like:

- 1) Citric acid cycle
- 2) Oxidative phosphorylation

#### 5. Citric Acid Cycle

It is also known as “kreb’s cycle or TCA cycle”. This metabolic pathway has been discovered by “Hans Krebs”. It involves in the breakdown of acetyl co-A, which has been obtained by the dehydrogenase of pyruvate. In which, pyruvate dehydrogenase enzyme has been involved in breaking down of pyruvate to acetic acid in the form of acetyl co-A. Enormous amount of energy in the form of ATP i.e. about 38 ATP molecules has been released along with some precursors of amino acids. In addition to it 10 “NADH” which is a reducing agent, 2 FADH<sub>2</sub>, water and carbon dioxide are also released as an end product of kreb’s cycle. This reducing agent NADH and FADH<sub>2</sub> involves in oxidative phosphorylation. This metabolic pathway takes place in the matrix region of mitochondria which is an aerobic reaction.

prokaryotes, it takes place in plasma membrane. This reaction involves in oxidation of NADH and FADH<sub>2</sub> which are the end product of kreb’s cycle. During oxidation, protein complex provides protons for pumping of electrons. At the end of this reaction, oxygen accepts 2 protons and forms water (H<sub>2</sub>O). Thus oxygen is known as terminal electron acceptor. Protein complex which involves are cytochrome B, cytochrome a, cytochrome c, cytochrome B6 etc.... which are also termed as complex I, complex II, complex III, complex IV and complex V. These complexes of proteins are assembled on the membrane. As a result, 30 ATP molecules are generated by oxidizing NADH and 4 ATP molecules have been generated from FADH<sub>2</sub>. Totally 34 molecules of ATP are generated through electron transport chain.

#### Chemiosmosis

As a result of electron transport chain, a high concentration of protons is generated in the membrane. Thus, through ATP synthase channel in the membrane, these protons flow through these channels thus generate energy in the form ATP. This is known as chemiosmosis. This happens because; when the protons flow from higher concentration to lower concentration it helps ATP synthase to synthesis ATP by adding phosphate to ADP(Adenosine di-phosphate).

#### Mitochondrial Related Diseases

Some of the mitochondrial diseases are likely to be discussed in this review article. They are:

##### 1) Lhon Disease

It is also called as Leber’s Hereditary Optic Neuropathy (LHON). It is commonly seen in both men and women at the age of 20, but it is mostly seen in men than women. It majorly affects central vision.

**Symptoms:**

- Painless blurriness in one eye
- Disk hyperemia
- Edema of retinal
- But it is mostly asymptomatic

**Causes:**

- Genetic inheritance from mother
- Leads to cell damage in optic nerve cells

**Treatment:**

- Genetic counselling
- Prenatal diagnosis

**2) Leigh Disease**

It is characterised as neuro-metabolic disorders. It leads to lesions on the brain, mid brain and brainstem. It affects all age group people but most common in infants. It is found 1 in 40,000 births. It is caused due to mutation in 75 different genes i.e. 20% of mtDNA, this leads to disruption of protein complex that involves in oxidative phosphorylation. This disease results in short life span of affected infant.

**Symptoms:**

- Loss of mental development like talking, walking and even vomiting
- Loss of appetite
- Symptoms are seen few months later from birth.

**3) Pyruvate Dehydrogenase Complex Deficiency**

It is characterised by poor muscle tone and neurological damage. This is due to lactic acid production which is caused by defected gene PDHA 1 is located in X-chromosome. When carbohydrate does not get breakdown into ATP, it leads to the production of lactic acid. This disease has been found to be recessive inheritance.

**Symptoms:**

- Low blood pressure
- Vomiting
- High heart rate
- Rapid breathing
- Poor muscle tone

**4) Autosomal Dominant Optic Atrophy (ADOA):**

It is an autosomal inherited disease affects optic nerves. It has been caused by OPAI gene in chromosome 3. It affects individual in childhood.

**Symptoms**

- Blindness

**5) Kearns Sayre Syndrome**

It is an autosomal inheritance disease which affects at the age of 20 years. It is characterised as myopathy.

**Symptoms:**

- Difficulty in opening eyelids
- Pigmentation of retina