
Mitochondrial medicine - a key to solve pathophysiology of XXI century diseases

Emina Kiseljaković, Radivoj Jadrić, Sabaheta Hasić, Lorenka Ljuboja, Jovo Radovanović, Husein Kulenović and Mira Winterhalter-Jadrić

Institute for Physiology and Biochemistry, Department of Biochemistry, Faculty of Medicine, Sarajevo

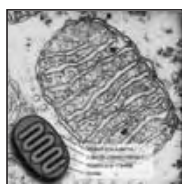
Abstract

Over the past 13 years mitochondrial defects have been involved in wide variety of degenerative diseases — Parkinson disease, Alzheimer dementia, arteriosclerosis, ageing and cancer. Mitochondria are believed to control apoptosis or programmed cell death. Disturbance in mitochondrial metabolism has also been implicated in many common diseases such as congestive heart failure, diabetes and migraine. Scientific investigations have showed complexities in mitochondrial genetics, but at the same time, pathophysiology of mitochondrial diseases is still enigma. Mitochondria and their DNAs are opening the era of “mitochondrial medicine”. What we today call “a mitochondrial medicine” is only a part of the whole panorama of diseases based on disordered mitochondrial function.

Keywords: mitochondria, mtDNA, mitochondrial diseases

Abbreviations: mtDNA — mitochondrial DNA, ATP - adenosine triphosphate, OXPHOS - oxidative phosphorylation

Introduction



It is interesting to note that the first cell organelle ever to be linked to a human disease was a mitochondrion. In 1962, Luft and his co-workers presented evidence of mitochondrial dysfunction in one patient - a 27-years old woman with the highest oxygen consumption ever recorded. She had a hypermetabolic state, structurally abnormal mitochondria and abnormalities in oxidative phosphorylation. Involvement of the thyroid gland was excluded. This rare disorder is known as Luft's diseases.

Almost eight years had passed before a few other patients were reported with aberrations of mitochondrial function, although with quite different symptoms. In the meantime, a specific mitochondrial DNA was discovered in 1964. Nothing happened until 1988 when a new revolution in mitochondrial pathophysiology came onto scene, according to the report of an association of different sporadic encephalomyopathies with large deletions of mtDNA. This group of diseases - genetic mitochondrial disorders due to mutations in mtDNA and dysfunction in electron transport — have expanded dramatically during previous

13 years. This small mtDNA has become a Pandora's box of pathogenic mutation (1). Now, there are more than 100 different pathogenic mtDNA pointed mutations and 200 mtDNA deletions and insertions linked to the different human diseases (2). In addition, several lines of evidence have suggested that mitochondrial dysfunctions may play a role in the ageing process, as well as in some of the most common age-related disorders e.g. heart failure, some neurodegenerative diseases and diabetes mellitus (3).

Mitochondrial genome and mtDNA genetics

Mitochondria are cytoplasmic organelles with double-membrane and they are responsible for cellular energy production. Adenosine triphosphate (ATP) is produced in mitochondria in metabolic process known as oxidative phosphorylation (OXPHOS). OXPHOS carries out by five respiratory chain complexes located within the mitochondrial inner membrane. This chain is a line of protein complexes that combines electron with oxygen to generate potential energy in the form of ATP. A numerous proteins of respiratory chain are encoded by two genetic systems - nuclear DNA and mitochondrial DNA.

Mitochondrial DNA (mtDNA) is 16.569-nucleotide pair, double stranded circular chromosome located in mitochondrial matrix (4).

Genetic characteristics of mtDNA are:

- Maternal inheritance - mother transmits her oocyte mtDNA to the offspring. Male gamete does not contribute the inheritance process.
- Polyploidy - each human cell has a hundreds of mitochondria each containing several mtDNAs.
- Heteroplasmy - if mutated mtDNA coexist in the same tissue with normal-wild type mtDNA that is heteroplasmy.
- High mutation rate - 10-20 times higher mutation rate in mtDNA than in the nuclear DNA.

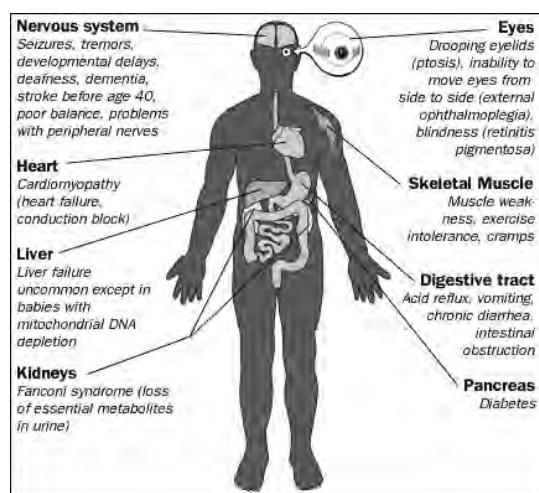
For the further information highly recommended web pages are:

Mitomap <http://www.gen.emory.edu/mitomap.html/>
GOBASE <http://megasun.bch.umontreal.ca/gobase/>

Mitochondrial diseases

Mitochondria are essential for the food we eat turning into energy in the form of ATP. Mitochondrial diseases result from the failure of mitochondria to create energy (mitochondria are responsible for the creating of more than 90% of energy needed by the cell). When they fail, less energy is generated, the whole system is beginning to suffer and life is severely compromised. Mitochondrial disease primarily affects children while in adults it becomes more common.

Commonly Affected Systems in Mitochondrial Disorders



The main problems associated with mitochondrial diseases - low energy, free radical production and lactic acidosis - can result in the variety of symptoms of many different organs of the body. This diagram shows common symptoms of mitochondrial diseases, of which, most people have a specific spectrum (5).

Table 1 presents some of disorders that can be caused by the mutations of mitochondrial DNA. Nuclear mutations or other processes that disrupt mitochondrial function can also cause these medical conditions. (6)

All of these problems start when something goes wrong in mitochondria. Some of them are direct result of the interruption in energy supply, while others may develop as a consequence to secondary build-up of toxic by-products.

Mitochondria play a central role in regulation of the programmed cell death -apoptosis. These organelles can trigger cell death in many ways - by disruption of the electron transport and energy metabolism or by the activation of proteins that mediate process. This mechanism may be an explanation of how mitochondria and their functions contribute to the pathogenesis of human diseases.

During the last 13 years we have witnessed the enormous growth of mitochondrial medicine. New investigative techniques have continuously been adopted. Mitochondrial DNA mutations have been successfully linked to diseases and disorders affecting virtually every system of the human body. Many linkages have been discovered recently, suggesting that in the future even more

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| Alzheimer's disease | Progressive loss of cognitive capacity |
| CPEO (chronic progressive external ophthalmoplegia) | Paralysis of eye muscles and mitochondrial myopathy |
| Diabetes mellitus | High blood glucose levels and various complications |
| Dystonia | Abnormal movements, muscular rigidity; frequently accompanied by degeneration of the basal ganglia of the brain |
| KSS (Kearns-Sayre syndrome) | CEO combined with retinal deterioration, heart disease, hearing loss, diabetes and kidney failure |
| Leigh's syndrome | Progressive loss of motor and verbal skills and degeneration of the basal ganglia; a potentially lethal childhood disease |
| LHON (Leber's hereditary optic neuropathy) | Permanent or temporary blindness stemming from damage to the optic nerve |
| MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes) | Dysfunction of brain tissue (causing seizures, transient regional paralysis and dementia) combined with mitochondrial myopathy and a toxic level of acid lactic and acidosis in the blood |
| MERRF (myoclonic epilepsy and ragged red fibres) | Seizures with mitochondrial myopathy, may involve hearing loss and dementia |
| Mitochondrial Myopathy | Deterioration of muscle, manifested by weakness and intolerance for exercise; muscle often displays ragged red fibres, which are filled with abnormal mitochondria that turn red when exposed to a particular stain |
| NARP (neurogenic muscle weakness and retinitis pigmentosa) | Loss of muscle strength and coordination, accompanied by regional brain degeneration, ataxia and deterioration of the retina |
| Pearson's syndrome | Childhood bone marrow dysfunction (leading to loss of blood cells) and pancreatic failure |

diseases may be linked to the mitochondria. If mitochondria are the root for even more diseases, further research-

es of mtDNA could hold the answers to the origin of many diseases that plague XX and XXI centuries.

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