Mitochondrial DNA and Inherited Diseases – A Comprehensive Review

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Mitochondria are membrane-bound organelles located in the cytoplasm of the cell. They are the sites of cellular respiration which ultimately generates fuel for the cell's activities. Mitochondria are the only non-nuclear constituents of the cell with their own DNA (mtDNA) and machinery for synthesizing RNA and proteins. Mutations in the mitochondrial genome have been implicated with a wide range of age-related pathologies, cancers, neurodegenerative diseases and in general, processes that regulate cellular and organismal aging. There has been considerable progress in understanding the role of mtDNA mutations in human diseases during the last two decades, but important mechanisms in mitochondrial genetics remain to be explained at the molecular level. This review gives an overview of mitochondrial DNA structure and function and then outlines more specifically the metabolic and molecular alterations in mitochondria, associated with human diseases and their clinical implications.

Key words: Mitochondrial DNA, Somatic Mutations, Endosymbiotic Theory, Ageing, Neurodegenerative Disorders, Myopathies

INTRODUCTION

Mitochondria are sub cellular organelles that are found in the cytoplasm of the eukaryote cells and their principal function is the production of cellular energy. Mitochondria provide about 90 percent of the energy that cells-and thus tissues, organs and the body as a whole-need to function. They convert the energy from food into a form that cells can use, and are hence referred to as the "powerhouses". Mitochondria produce energy through a process called oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. Each cell contains hundreds to thousands of mitochondria. One of the particularities of these organelles is that they have a genetic system of their own with all the machinery necessary for their expression; that is, to replicate, transcribe and translate the genetic information they contain. This genetic material is known as mitochondrial DNA or mtDNA.

Origin and History:

Mitochondrial genome consist of a single circular molecule of DNA that resembles that of bacteria not that of the nuclear genome. Mitochondria have striking similarities to bacteria cells. This fact can be explained by endosymbiotic theory. The endosymbiosis theory postulates that the mitochondrion of eukaryotes were evolved from aerobic bacteria living within their host cell. Symbiosis occurs when two different species benefit from living and working together. When one organism actually lives inside the other it's called endosymbiosies. The endosymbiotic theory describes how a large host cell and ingested bacteria could easily become dependent on one another for survival, resulting in a permanent relationship. Over millions of years of evolution, mitochondria have become more specialized and today they cannot live outside the cell. A double membrane that surrounds mitochondria further provides evidence that they were ingested by a primitive host. The organelles also reproduce like bacteria, replicating their own DNA and directing their own division.

Inheritance:

mtDNA is typically passed on only from the mother. This means that there is little change in the mtDNA from generation to generation, unlike nuclear DNA which is inherited from both the Mother and Father and changes by 50% each generation. Human eggs are full of mitochondria, while sperm have only a hundred or so, just enough to power it while it swims towards the egg. Mitochondria in the sperm from the father are typically destroyed by the female egg cell immediately after fertilization, leaving behind only mtDNA from the mother. It was reported that paternal sperm mitochondria (containing mtDNA) are marked with ubiquitin to select them for later destruction inside the embryo. Therefore the mother's mtDNA is passed on to the next generation; the father’s typically not. Many researchers believe that mtDNA is better suited to identification of older skeletal remains than nuclear DNA because the greater number of copies of mtDNA per cell increases the chance of obtaining a useful sample, and because a match with a living relative is possible even if numerous maternal generations separate the two. Mitochondrial DNA is most useful in connecting the maternal lines of living people in different parts of the world. They join up with the clan mothers from other parts of the world and ultimately coalesce in one woman – mitochondrial Eve, who lived in Africa about 150 000 years ago. Wherever we live on the planet, we are all her descendants.

Structure of mtDNA:

A mitochondrion contains between 2–10 copies of mtDNA. Human mitochondrial DNA is a circular double-stranded molecule, 16,569 base pairs (bp) in length. It contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. All 13 polypeptides are components of the respiratory chain, including seven subunits of complex I (NADH dehydrogenase-ubiquinone oxidoreductase), one subunit of complex III (ubiquinone-cytochrome c oxidoreductase), three subunits of complex IV (cytochrome c oxidase), and two subunits of complex V (ATP synthetase). The remaining genes

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Mitochondrial Diseases:
Mitochondrial disorders may be caused by mutations, acquired or inherited, in mitochondrial DNA (mtDNA) or in nuclear genes that code for mitochondrial components. Oxidative phosphorylation (OXPHOS) is composed of five intramitochondrial enzyme complexes (complexes I to V) that are responsible for producing the majority of the ATP required for normal cellular function. Assembly and maintenance of OXPHOS requires the coordinate regulation of nuclear DNA and mitochondrial DNA (mtDNA) genes. The age-related accumulation of mtDNA mutations may contribute to the decline of cellular OXPHOS function with age and to the progression of a variety of degenerative diseases. Increases in somatic mtDNA mutations are associated with increased generation of free radicals that permanently damage the mtDNA. Once mtDNA damage occurs, the mutated mtDNA can persist in the cell and clonally proliferate over time. After sufficient levels of mutant mtDNA are reached, OXPHOS function begins to decline. Mitochondrial disease may become clinically apparent once the number of affected mitochondria reaches a certain level; this phenomenon is called “threshold expression”.

Role in Ageing:
Normally, ATP production is coupled to oxygen consumption. During abnormal states such as fever, cancer, or stroke, or when dysfunction occurs within the mitochondria, more oxygen is consumed or required than is actually used to make ATP. The mitochondria become partially “uncoupled” and produce highly reactive oxygen species called free radicals. When the production of free radicals overwhelms the mitochondria’s ability to “detoxify” them, the excess free radicals attack our mitochondria and mutate our mitochondrial DNA. This random accumulation of somatic mitochondrial DNA mutations would ultimately reduce energy output below needed levels in one or more tissues. These somatic mutations and mitochondrial inhibition could contribute to common signs of normal aging, such as loss of memory, hearing, vision and stamina. In persons whose energy output was already compromised due to inherited mitochondrial or nuclear mutations or by toxins or other factors, the resulting somatic mitochondrial DNA injury would push energy output below desirable levels more quickly. These individuals would then display symptoms earlier and would progress to full-blown disease more rapidly.

Mitochondrial Myopathy and Encephalomyopathy:
Mitochondrial myopathies are a group of neuromuscular diseases caused by damage to the mitochondria. The main symptoms of mitochondrial myopathy are muscle weakness and wasting, and exercise intolerance. ATP derived from mitochondria provides the main source of power for muscle cell contraction and nerve cell firing. So, muscle cells and nerve cells are especially sensitive to mitochondrial defects. The combined effects of energy deprivation and toxin accumulation in these cells probably give rise to the main symptoms of mitochondrial myopathies and encephalomyopathies. The most common syndromes include:
- Kearns-Sayre Syndrome (KSS)
- Leigh syndrome
- Mitochondrial DNA depletion syndrome (MDS)
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Myoclonus epilepsy with ragged red fibers (MERRF)
- Mitochondrial neuro gastro intestinal encephalo myopathy (MNGIE)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- Progressive external ophthalmoplegia (PEO)

The symptoms of mitochondrial myopathies include muscle weakness or exercise intolerance, heart failure or rhythm disturbances, dementia, movement disorders, stroke-like episodes, deafness, blindness, droopy eyelids, limited
mobility of the eyes, vomiting, and seizures. The prognosis for these disorders ranges in severity from progressive weakness to death. Most mitochondrial myopathies occur before the age of 20, and often begin with exercise intolerance or muscle weakness. During physical activity, muscles may become easily fatigued or weak. Muscle cramping is rare, but may occur. Nausea, headache, and breathlessness are also associated with these disorders.

A mitochondrial encephalomyopathy includes some of the above-mentioned symptoms of myopathy plus one or more neurological symptoms. Again, these symptoms show a great deal of individual variability in both type and severity. Hearing impairment, migraine-like headaches and seizures are among the most common symptoms of mitochondrial encephalomyopathy. In at least one syndrome, headaches and seizures often are accompanied by stroke-like episodes. Fortunately, there are good treatments for some of these conditions. Hearing impairment can be managed using hearing aids and alternate forms of communication. Often, headaches can be alleviated with medications, and seizures can be prevented with drugs used for epilepsy (anti-epileptics).

Neurodegenerative Disorders:
Alzheimer’s disease (AD) and Parkinson’s disease (PD) are common devastating neurodegenerative disorders, affecting many elderly people worldwide. Although they both constitute distinct entities they share some features. The overlapping phenotypic features of AD and PD implicate related etiological mechanism. Epidemiological data indicates that the risk of developing AD and PD is greater for a person whose mother was affected by the disease in comparison with an offspring of an affected father. It is accepted that inherited somatic mutations can contribute to these diseases.

Alzheimer’s Disease:
Mutations in the genes for amyloid precursor protein or presenilin 1 and 2 are associated with familial Alzheimer’s disease (AD). Amyloid (AB) can inhibit OXPHOS in mitochondria. Defects in mitochondrial oxidative phosphorylation have frequently been associated with Alzheimer’s disease (AD), and both inherited and somatic mtDNA mutations have been reported in certain AD cases. To determine whether mtDNA mutations contribute more generally to the etiology of AD, the sequence of the mtDNA control region (CR) from AD brains have been investigated for possible disease-causing mutations. Sixty-five percent of the AD brains harbored the T414G mutation, whereas this mutation was absent from all controls. Moreover, cloning and sequencing of the mtDNA CR from patient and control brains revealed that all AD brains had an average 63% increase in heteroplasmic mtDNA CR mutations. In addition, these mutations preferentially altered known mtDNA regulatory elements. Certain AD brains harbored the disease-specific CR mutations T414C and T477C, and several AD brains between 74 and 83 years of age harbored the CR mutations T477C, T146C, and T195C, at levels up to 70–80% heteroplasmacy. AD patient brains also had an average 50% reduction in the mtDNA L-strand NDS transcript and in the mtDNA/nuclear DNA ratio. Because reduced ND6 mRNA and mtDNA copy numbers would reduce brain oxidative phosphorylation, these CR mutations could account for some of the mitochondrial defects observed in AD.

Parkinson’s disease:
Parkinson’s disease (PD) is the second most common progressive neurodegenerative condition. The main pathological feature of PD is a substantial loss of dopaminergic neurons in substantia nigra and formation of intracellular proteinaceous inclusion called Lewy bodies. The relation between Parkinson’s disease (PD) and mitochondria was first established with the identification of a deficiency in the activity of complex I in PD substantia nigra and subsequently in the peripheral tissues of patients. Complex I is the target of toxins known to produce parkinsonian features in people, such as MPTP and annonacin. Inhibition of complex I results in increased free radical generation and could contribute to the oxidative mediated damage seen in the PD nigra. The pathogenesis of PD also includes protein aggregation (Lewy bodies). Mitochondrial dysfunction will contribute to dysfunction of the energy-dependent ubiquitin proteasomal system (UPS), and oxidative stress will add to the substrate load. This combination has been shown to enhance dopaminergic cell damage and death. Occasional mtDNA point mutations have been identified in PD but these have not been present in the general PD population. Thus, their association with PD might merely represent part of the wide clinical spectrum of mtDNA mutations and not necessarily imply a more common role in sporadic PD. A mutation in the mtDNA 12S RNA was identified in a patient with maternally inherited early onset PD, deafness, and neuropathy. Several studies that have sequenced mtDNA in PD patients have not identified any consistent mutations.

Type 2 Diabetes:
Diabetes is a diseases characterized by the presence of chronic hyperglycemia. Maintenance of normal glucose homeostasis involves the action of a glucose sensor in the pancreatic β-cell that detects an increase in blood glucose concentration and converts that into increased secretion of insulin. Increased circulating insulin concentrations suppress hepatic glucose output and stimulate glucose uptake by muscle and adipose tissue. Pathophysiological mechanisms leading to diabetes can involve an inappropriate secretion of insulin, insulin resistance of the liver, muscle and fat or combined defects. The risk of an individual to develop diabetes involves a complex interaction between genetic and environmental factors. Mitochondria are main producers of reactive oxygen species (ROS) inside cells. The amount of ROS contributes to apoptosis and probably also to the differentiation state of pancreatic β-cells. Pancreatic β-cells have a poor regeneration capacity when cells are lost. Thus, under conditions of enhanced loss of β-cells, either by apoptosis or dedifferentiation, a situation will emerge in which insufficient replacement takes place of lost β-cells. This will result in inadequate insulin secretion to maintain correct glucose homeostasis. It is well recognized that in some families diabetes follows a maternal inheritance pattern, and that there is an excess of maternal transmission in type 2 diabetes. As mitochondrial DNA (mtDNA) is passed exclusively down the maternal line, it was postulated that mtDNA defects might contribute to the excess maternal transmission. This was subsequently confirmed, and a number of mtDNA defects have been implicated in the development of diabetes. An A to G substitution at position A3243G in the tRNA-Leu(UUR) gene is the most commonly reported defect associated with diabetes.
Cancer: Mitochondria have been implicated in the process of carcinogenesis because of their vital role in energy production, nuclear-cytoplasmic signal integration and control of metabolic pathways. During neoplastic transformation there is an increase in reactive oxygen species, which damages the mitochondrial genome. This accelerates the somatic mutation rate of mitochondrial DNA. It has been proposed that these mutations may serve as an early indication of potential cancer development and may represent a means for tracking tumor progression. Mutations have been detected in mitochondria of different tumor types, including breast, colon, esophageal, endometrial, head and neck, hepatocellular, kidney, leukemia, lung, melanoma, oral, prostate, and thyroid cancer. However, it is not clear whether mitochondrial genomic status in human cells affects nuclear genome stability and whether proteins involved in intergenic cross talk are involved in tumorigenesis.

Somatic mitochondrial mutations are common in human cancers, and can be used as a tool for early detection of cancer. The majority of these somatic mutations are homoplasmic in nature, indicating that the mutant mtDNA become dominant in tumor cells. For instance germline mtDNA mutations at nucleotides 10398 and 16189 have been associated with breast cancer and endometrial cancer. Tumor mtDNA somatic mutations range from severe insertion-deletion and chain termination mutations to mild missense mutations.

Male Infertility: Infertility affects about 15 per cent married couples half of which may be attributed to men with low sperm motility (asthenozoospermia), low sperm count (oligozoospermia) or abnormal sperm morphology (teratozoospermia)49. As mitochondria supply energy by OXPHOS for initiation, differentiation and function of the germ cells, any mutation in mtDNA disrupts adenosine triphosphate (ATP) production and thus result in an impaired spermatogenesis and impaired mitochondrial DNA (mtDNA) play an important role in the development of disorders that afflict many people in their later years, such as diabetes, deafness, heart disease, muscle weakness, movement problems and aging. Certain mitochondrial DNA mutations have been proved to cause some fraction of cases of Alzheimer’s disease, Parkinson’s disease, dystonia (a progressive movement disorder) and other neurodegenerative diseases.33 These patterns combined with the fact that a number of late-life degenerative diseases have been associated with declines in the activity of protein complexes involved in energy production suggest that progressive reductions in mitochondrial energy (ATP) production, increased generation of reactive oxygen species and impaired calcium buffering in nerve, muscle or other tissues could be an important contributor to aging and to various age-related degenerative diseases52.

It is clearly evident that free-radical damage drives the accumulation of somatic mitochondrial DNA mutations and thus influences the speed of aging and other related diseases. So treatments that block mitochondrial production of such radicals and thereby protect mitochondrial DNA could potentially slow aging and delay the onset of age-related diseases. Such approaches could perhaps consist of lifelong treatment with antioxidants. To that end, scientists are attempting to clarify the molecular interactions by which nuclei detect local energy deficits and stimulate the reproduction of aberrant mitochondria in their neighborhood. Evidence based research shows that mutations in mitochondrial DNA have been implicated in dozens of mysterious disorders as well as in aging and a variety of chronic degenerative diseases. Today studies on this DNA offers new clues to the development of many ailments and suggests approaches to treat them and prevent their progression.

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