THE MITOCHONDRIAL RESPIRATORY CHAIN

The human mitochondrial genome is a tiny circle of double-stranded DNA 16,569 base pairs (bp) in length. It contains 37 genes, which specify 2 ribosomal RNAs (rRNAs), 22 transfer RNAs (tRNAs), and 13 polypeptides, all of which are components of complexes of the respiratory chain/oxidative phosphorylation system.
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Mitochondrial genetics is unusual in many ways. First, mitochondria and mtDNAs are unique in that they are inherited only from the mother. Thus, most pathogenic errors in mtDNA are maternally-inherited: women will transmit the defect to all of their children (both boys and girls), but only the daughters will transmit the disease to their children. Second, cells contain hundreds or thousands of mitochondria; each mitochondrial contains approximately 5 mtDNAs. Thus, both normal and mutated mtDNAs may coexist within the patient's tissues, a condition known as heteroplasmy. If the patient is heteroplasmic, the clinical phenotype can vary among tissues and can even change within a tissue during the course of time, due to the random distribution of mutated mtDNAs to daughter cells during each cell division; this phenomenon is known as mitotic segregation. Virtually every human organ system can be affected, but tissues with high requirements for oxidative energy metabolism, such as muscle, heart, eye, and brain, are particularly vulnerable; this is referred to as the threshold effect. Relatively low levels of mutated mtDNAs can affect the respiratory capacity of these tissues, and high levels can be extremely devastating. It is therefore no surprise that mitochondrial disorders effect predominantly muscle and brain encephalomyopathies.
The human mitochondrial genome

Special features of mitochondrial genetics

The cytoplasmic location of mtDNA and the high copy number contribute to certain unique features of mitochondrial genetics. First, mtDNA is maternally inherited. Second, mtDNA genes have a much higher mutation rate than nuclear DNA genes. Third, mitochondria undergo replicative segregation at cell division. Fourth, many of the pathogenic mtDNA mutations are heteroplasmic. For expression of a disease it is required that a certain threshold level of mutant mtDNA should be exceeded. Fifth, somatic mtDNA mutations accumulate in post-mitotic tissues with age, reducing the ATP generating capacity.

Maternal inheritance

MtDNA is maternally inherited. The mammalian egg contains about 100,000 molecules of mtDNA, while the sperm contains of the order of 100–1500 mtDNAs. Sperm mitochondria enter the egg during fertilization but they appear to be lost early in embryogenesis, soon after fertilization, between the two-cell and four-cell stages.

High mutation rate

Mitochondria seem to lack an efficient DNA repair system. Moreover, protective proteins such as histones are missing and mtDNA is physically associated with the inner mitochondrial membrane, where highly mutagenic oxygen radicals are generated as by-products of OXPHOS. These unique features are probably the cause of the about 10 to 17 times faster accumulation of polymorphisms in mtDNA than in nuclear DNA. The hypervariable sequences in the D-loop evolve even more rapidly than the coding regions.

Replicative segregation

Each cell has hundreds of mitochondria, each containing 2 to 10 copies of mtDNA molecules. Normally all mtDNAs in a cell are identical, a condition known as homoplasmy. At cell division, the mitochondria and their genomes are randomly distributed to the daughter cells, a process known as replicative segregation. When a mutation arises in mtDNA, it creates an intracellular mixture of mutant and normal molecules, a condition known as heteroplasmy. Despite the high mtDNA copy number in mature oocytes and the relatively small number of cell divisions in the female germline, mtDNA sequence variants segregate rapidly between generations.
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Special features of mitochondrial genetics

Age-related somatic mtDNA mutations
Oxygen free radicals damage mtDNA, causing oxidative modifications of DNA bases, base substitutions and rearrangements. The cumulative accumulation of these somatic mutations during life may cause a bioenergetic deficit leading to cell death, or apoptosis, and normal ageing. In addition to the ageing or senescence process somatic mtDNA mutations may be important for determining the onset and progression of mtDNA diseases. Most inherited mutations are insufficient to suppress mitochondrial OXPHOS below the expression threshold and thus it is the accumulation of somatic mutations in postmitotic tissues that exacerbates the inherited OXPHOS defect and ultimately leads to phenotypic expression. Oxidative stress has been implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease. There is much evidence of increased oxidative stress and free radical damage in the substantia nigra in patients with Parkinson’s disease, and there is also evidence for a defect in mitochondrial energy production, and especially reduced complex I activity, in the substantia nigra.
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Complex I  Complex II  Complex III  Complex IV  Complex V  F$_{1}$F$_{0}$ ATP synthase
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Ageing and longevity

Ageing Theories

- Free Radical Theory
- Mitochondria and Ageing
- Glycation Theory of Ageing
- Protein Damage and Maintenance
- DNA Damage and DNA Repair
- Telomeres and Ageing
- Cellular Senescence and Apoptosis
- Longevity Genes
- Sirtuins and Deacetylases
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