85e Mitochondrial DNA and Heritable Traits and Diseases

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Mitochondria are cytoplasmic organelles whose major function is to generate ATP by the process of oxidative phosphorylation under aerobic conditions. This process is mediated by the respiratory electron transport chain (ETC) multiprotein enzyme complexes I–V and the two electron carriers, coenzyme Q (CoQ) and cytochrome c. Other cellular processes to which mitochondria make a major contribution include apoptosis (programmed cell death) and additional cell type–specific functions (Table 85e-1). The efficiency of the mitochondrial ETC in ATP production is a major determinant of overall body energy balance and thermogenesis. In addition, mitochondria are the predominant source of reactive oxygen species (ROS), whose rate of production also relates to the coupling of ATP production to oxygen consumption. Given the centrality of oxidative phosphorylation to the normal activities of almost all cells, it is not surprising that mitochondrial dysfunction can affect almost any organ system (Fig. 85e-1). Thus, physicians in many disciplines might encounter patients with mitochondrial diseases and should be aware of their existence and characteristics.

The integrated activity of an estimated 1500 gene products is required for normal mitochondrial biogenesis, function, and integrity. Almost all of these are encoded by nuclear genes and thus follow the rules and patterns of nuclear genomic inheritance (Chap. 84). These nuclear-encoded proteins are synthesized in the cell cytoplasm and imported to their location of activity within the mitochondria through a complex biochemical process. In addition, the mitochondria contain their own small genome consisting of numerous copies (polyploidy) per mitochondrion of a circular, double-strand mitochondrial DNA (mtDNA) molecule comprising 16,569 nucleotides. This mtDNA sequence (also known as the "mitogenome") might represent the remnants of endosymbiotic prokaryotes from which mitochondria are thought to have originated. The mtDNA sequence contains a total of 37 genes, of which 13 encode mitochondrial protein components of the ETC (Fig. 85e-2). The remaining 22 tRNA- and 2 rRNA-encoding genes are dedicated to the process of translating the 13 mtDNA-encoded proteins. This dual nuclear and mitochondrial genetic control of mitochondrial function results in unique and diagnostically challenging patterns of inheritance. The current chapter focuses on heritable traits and diseases related to the mtDNA component of the dual genetic control of mitochondrial function. The reader is referred to Chaps. 84 and 462e for consideration of mitochondrial disease originating from mutations in the nuclear genome. The latter include (1) disorders due to mutations in nuclear genes directly encoding structural components or assembly factors of the oxidative phosphorylation complexes, (2) disorders due to mutations in nuclear genes encoding proteins indirectly related to oxidative phosphorylation, and (3) mtDNA depletion syndromes (MDS) characterized by a reduction of mtDNA copy number in affected tissues without mutations or rearrangements in the mtDNA.

TABLE 85e-1 FUNCTIONS OF MITOCHONDRIA

All Cells and Tissues
Oxidative phosphorylation
Apoptosis (programmed cell death)
Tissue- or Cell-Specific
Cholesterol metabolism
Amino and organic acid metabolism
Fatty acid beta oxidation
Sex steroid synthesis
Heme synthesis
Hepatic ammonia detoxification
Neurotransmitter metabolism

MITOCHONDRIAL DNA STRUCTURE AND FUNCTION

As a result of its circular structure and extranuclear location, the replication and transcription mechanisms of mtDNA differ from the corresponding mechanisms in the nuclear genome, whose nucleosomal packaging and structure are more complex. Because each cell contains many copies of mtDNA, and because the number of mitochondria can vary during the lifetime of each cell, mtDNA copy number is not directly coordinated with the cell cycle. Thus, vast differences in mtDNA copy number are observed between different cell types and tissues and during the lifetime of a cell. Another important feature of the mtDNA replication process is a reduced stringency of proofreading and replication error correction, leading to a greater degree of sequence variation compared to the nuclear genome. Some of these sequence variants are silent polymorphisms that do not have the potential for a phenotypic or pathogenic effect, whereas others may be considered pathogenic mutations.

With respect to transcription, initiation can occur on both strands and proceeds through the production of an intronless polycistronic precursor RNA, which is then processed to produce the 13 individual mRNA and 24 individual tRNA and rRNA products. The 37 mtDNA genes comprise fully 93% of the 16,569 nucleotides of the mtDNA in what is known as the *coding region*. The *control region* consists of ~1.1 kilobases (kb) of noncoding DNA, which is thought to have an important role in replication and transcription initiation.

MATERNAL INHERITANCE AND LACK OF RECOMBINATION

In contrast to homologous pair recombination that takes place in the nucleus, mtDNA molecules do not undergo recombination, such that mutational events represent the only source of mtDNA genetic diversification. Moreover, with very rare exceptions, it is only the maternal DNA that is transmitted to the offspring. The fertilized oocyte degrades mtDNA carried from the sperm in a complex process involving the ubiquitin proteasome system. Thus, although mothers transmit their mtDNA to both their sons and daughters, only the daughters are able to transmit the inherited mtDNA to future generations. Accordingly, mtDNA sequence variation and associated phenotypic traits and diseases are inherited exclusively along maternal lines.

As noted below, because of the complex relationship between mtDNA mutations and disease expression, sometimes this maternal inheritance is difficult to recognize at the clinical or pedigree level. However, evidence of paternal transmission can almost certainly rule out an mtDNA genetic origin of phenotypic variation or disease; conversely, a disease affecting both sexes without evidence of paternal transmission strongly suggests a heritable mtDNA disorder (Fig. 85e-2).

MULTIPLE COPY NUMBER (POLYPLOIDY), HIGH MUTATION RATE, HETEROPLASMY, AND MITOTIC SEGREGATION

Each aerobic cell in the body has multiple mitochondria, often numbering many hundreds or more in cells with extensive energy production requirements. Furthermore, the number of copies of mtDNA within each mitochondrion varies from several to hundreds; this is true of both somatic as well as germ cells, including oocytes in females. In the case of somatic cells, this means that the impact of most newly acquired somatic mutations is likely to be very small in terms of total cellular or organ system function; however, because of the manyfold higher mutation rate during mtDNA replication, numerous different mutations may accumulate with aging of the organism. It has been proposed that the total cumulative burden of acquired somatic mtDNA mutations with age may result in an overall perturbation of mitochondrial function, contributing to age-related reduction in the efficiency of oxidative phosphorylation and increased production of damaging ROS. The accumulation of such acquired somatic mtDNA mutations with aging may contribute to age-related diseases, such as metabolic syndrome and diabetes, cancer, and neurodegenerative and cardiovascular disease in any given individual. However, somatic mutations are not carried forward to the next generation, and the