Review

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Protecting the mitochondrial powerhouse

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Mitochondria are the oxygen-consuming power plants of cells. They provide a critical milieu for the synthesis of many essential molecules and allow for highly efficient energy production through oxidative phosphorylation. The use of oxygen is, however, a double-edged sword that on the one hand supplies ATP for cellular survival, and on the other leads to the formation of damaging reactive oxygen species (ROS). Different quality control pathways maintain mitochondria function including mitochondrial DNA (mtDNA) replication and repair, fusion–fission dynamics, free radical scavenging, and mitophagy. Further, failure of these pathways may lead to human disease. We review these pathways and propose a strategy towards a treatment for these often untreatable disorders.

Mitochondrial genetics

Mitochondria are a dynamic network of organelles constantly adapting their morphology and function to accommodate the needs of the cell. They are composed of an outer membrane, an intermembrane space, a highly folded inner membrane (the cristae), and a matrix space. Due to the prokaryotic origin of this organelle, the inner mitochondria membrane contains a specialized phospholipid, cardiolipin, that is also found in bacteria. More importantly, mitochondria contain their own DNA. The human mitochondrial genome, mtDNA, is a small circular ~16.6 kilobase molecule that resides inside the matrix space associated with the inner membrane of the mitochondria [1]. mtDNA in humans encodes 13 polypeptides, 22 tRNAs, and two ribosomal genes that are essential for oxidative phosphorylation, the metabolic process by which cells convert energy stored in a range of different substrates to ATP, which is the energetic currency of the organism. All of the remaining mitochondrial proteins, including gene products necessary for mtDNA replication, transcription, and DNA repair, are derived from nuclear genes and are imported into the mitochondria, typically, but not exclusively, via a mitochondrial targeting sequence [2]. In addition to the role of mitochondria in ATP production, this organelle is also central in apoptosis, heme and steroid synthesis, Ca^{2+} regulation, adaptive thermogenesis, and other processes. Proper mitochondrial function is therefore critical for organismal health.

An understanding of mtDNA inheritance and maintenance patterns is essential for comprehending mitochondrial dysfunction in disease. mtDNA is packaged into protein–DNA structures called nucleoids containing one or more mtDNA genomes within a single nucleoid. Additionally, there are a few to several thousand copies of mtDNA per cell varying with cell type [3]. Cells can simultaneously carry a mixture of normal and mutated mitochondrial genomes, a condition known as heteroplasmy. Mutant mtDNA can be propagated along with normal mtDNA, when there is no selection pressure against the mutant genome, thereby contributing to the high sequence evolution of mtDNA [4]. When a cell divides and the nucleoids are segregated between the two daughter cells, the proportion of mutant to normal mtDNA can shift [5]. This has important ramifications for mitochondrial disease since the relative proportion of mutant mtDNA molecules must reach a certain threshold before a disease phenotype is observed.

Bona fide primary mitochondrial diseases represent a heterogeneous group of disorders most often involving multiple organ systems leading to progressive degeneration and in many cases early death. Since the combined prevalence is estimated to be around 1:5000, a mitochondrial etiology should be considered when encountering any patient, particularly children, with multisystem pathology in tissues such as the central nervous system, heart, skeletal muscles, liver, and in rarer cases kidney [6]. The pathogenic mutation can be located either within the mitochondrial or nuclear genome and, as in the case of mutations in Twinkle or DNA polymerase γ (POLG), can give rise to a great diversity of clinical syndromes (Figure 1).

A number of well-defined syndromes are caused by maternally inherited mutations/deletions in mtDNA. Leigh syndrome is one of the most severe mitochondrial syndromes and can be caused by mutations in a number of mitochondrial as well as nuclear encoded genes. The patients usually die in infancy or early childhood due to rapidly progressing neurodegeneration [7]. Pearson syndrome is caused by inherited deletions in mtDNA [8]. This early childhood disease is characterized by lactic acidosis as well as pancreatic insufficiency and anemia, two clinical characteristics that are rare in other mitochondrial diseases. Interestingly, Pearson syndrome patients that survive through childhood may later develop Kearns–Sayre

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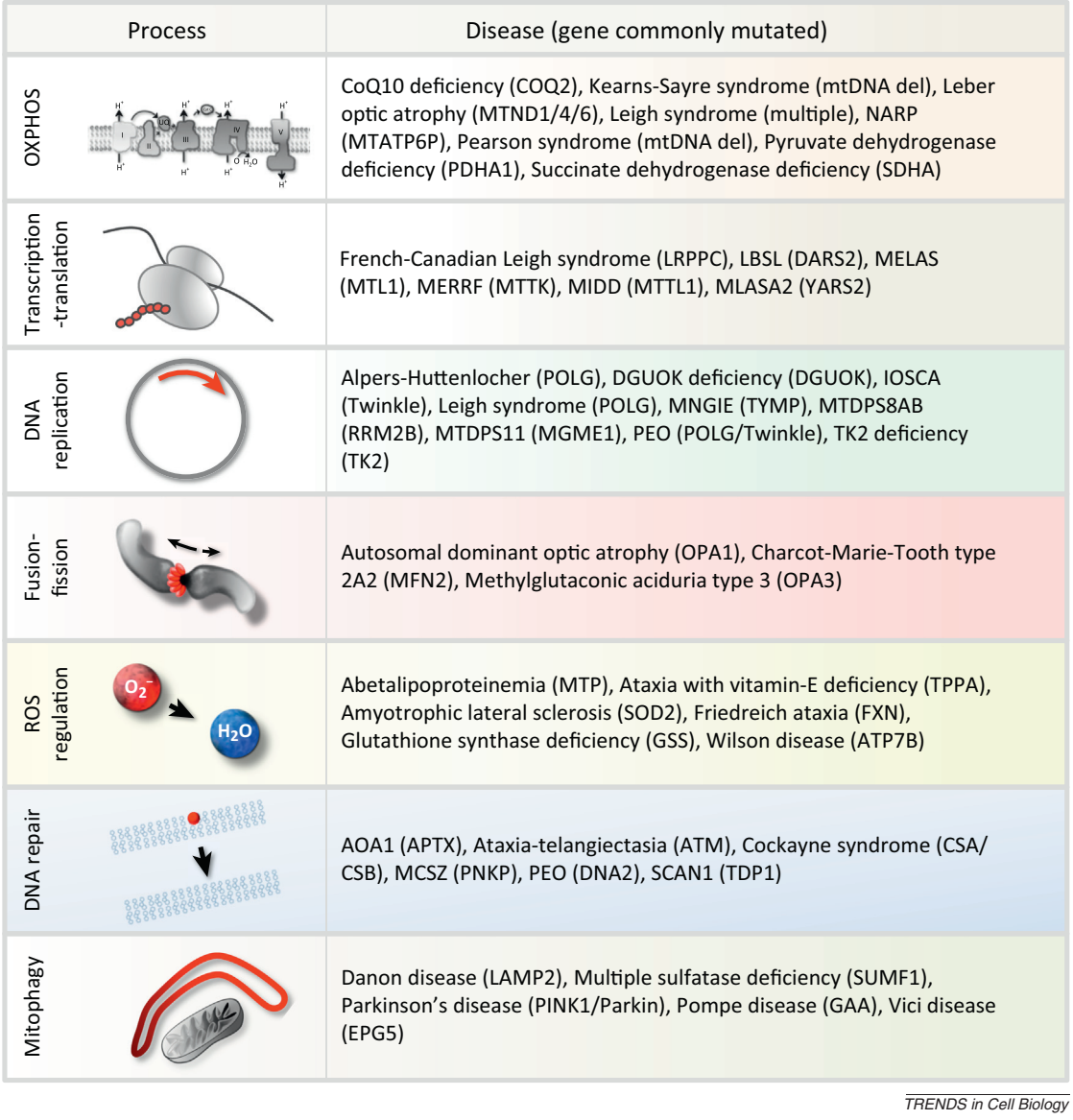

Figure 1. Examples of mitochondrial pathways that are associated with mitochondrial diseases.

syndrome, a disease characterized by ophthalmoplegia (loss of eye movement), retinal degeneration, and cardiomyopathy [9]. Other notable diseases caused by inherited mtDNA mutations are myoclonic epilepsy with ragged red fibers (MERRF) and myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). MERRF and MELAS are most commonly caused by mutations in the tRNA genes *MTTK* (mitochondrially encoded tRNA lysine) and *MTTL1* (mitochondrially encoded tRNA leucine 1), respectively, and there is often substantial overlap in the clinical presentation of the two syndromes [10,11]. Indeed, identical mutations in the mitochondrial genome can lead to both MERRF and MELAS as well as maternally inherited diabetes and deafness (MIDD). In addition, mtDNA mutations can lead to Leber's optic atrophy, neuropathy, ataxia, retinitis pigmentosum (NARP), as well as a number of other defined diseases. It is thus clear that an intact mitochondrial genome is essential for organismal fitness. In this review, we will attempt to explain the pathogenesis of mitochondrial disease based on the failure of a number of maintenance pathways that preserve the integrity of this crucial organelle.

Mitochondrial maintenance pathways

To preserve mtDNA integrity and mitochondrial function, several conserved pathways have evolved that are required for life (Figure 2). These include: (i) faithful DNA replication, transcription, and translation; (ii) processes that maintain redox homeostasis and prevent oxidative stress; (iii) systems that regulate proper mitochondrial fusion and fission; (iv) pathways that remove and repair mtDNA modifications; and (v) responses that eliminate excessively damaged mitochondria from the cell (i.e., mitochondrial autophagy/mitophagy). The importance of these pathways is underscored by the findings that defects in any of them can lead to human pathology. Notably, these pathways are highly regulated in particular by ROS that can signal fragmentation of the mitochondrial network [12], activation of antioxidant