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Review

Mutations that affect mitochondrial functions and their association with neurodegenerative diseases

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ABSTRACT

Mitochondria are essential for mammalian and human cell function as they generate ATP via aerobic respiration. The proteins required in the electron transport chain are mainly encoded by the circular mitochondrial genome but other essential mitochondrial proteins such as DNA repair genes, are coded in the nuclear genome and require transport into the mitochondria. In this review we summarize current knowledge on the association of point mutations and deletions in the mitochondrial genome that are detrimental to mitochondrial function and are associated with accelerated ageing and neurological disorders including Alzheimer's, Parkinson's, Huntington's and Amyotrophic lateral sclerosis (ALS). Mutations in the nuclear encoded genes that disrupt mitochondrial functions are also discussed. It is evident that a greater understanding of the causes of mutations that adversely affect mitochondrial metabolism is required to develop preventive measures against accelerated ageing and neurological disorders caused by mitochondrial dysfunction.

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1. Introduction

Mitochondria are intracellular organelles found in all mammalian nucleated cells and their main role is to produce cellular ATP by oxidative phosphorylation (OXPHOS). OXPHOS of fats and carbohydrates generates electrons which are transferred to oxygen via the redox component (complexes I–IV) found within the inner mitochondrial membrane to produce water. Protons are pumped across the inner membrane from the matrix to the intermembrane space forming an electrochemical gradient used by the fifth and terminal OXPHOS complex, the ATP synthase, to generate energy in the form of ATP. The biosynthesis and maintenance of normal respiratory chain complex function is dependent upon the co-ordinated expression and interaction of both the nuclear and mitochondrial (mtDNA) genomes.

The mitochondrial genome (Fig. 1) is a circular, double-stranded DNA molecule of 16.6 kb size (human) that encodes

Abbreviations: mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; ROS, reative oxygen species; AMD, age-related macular degeneration; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, Amyotrophic lateral sclerosis.

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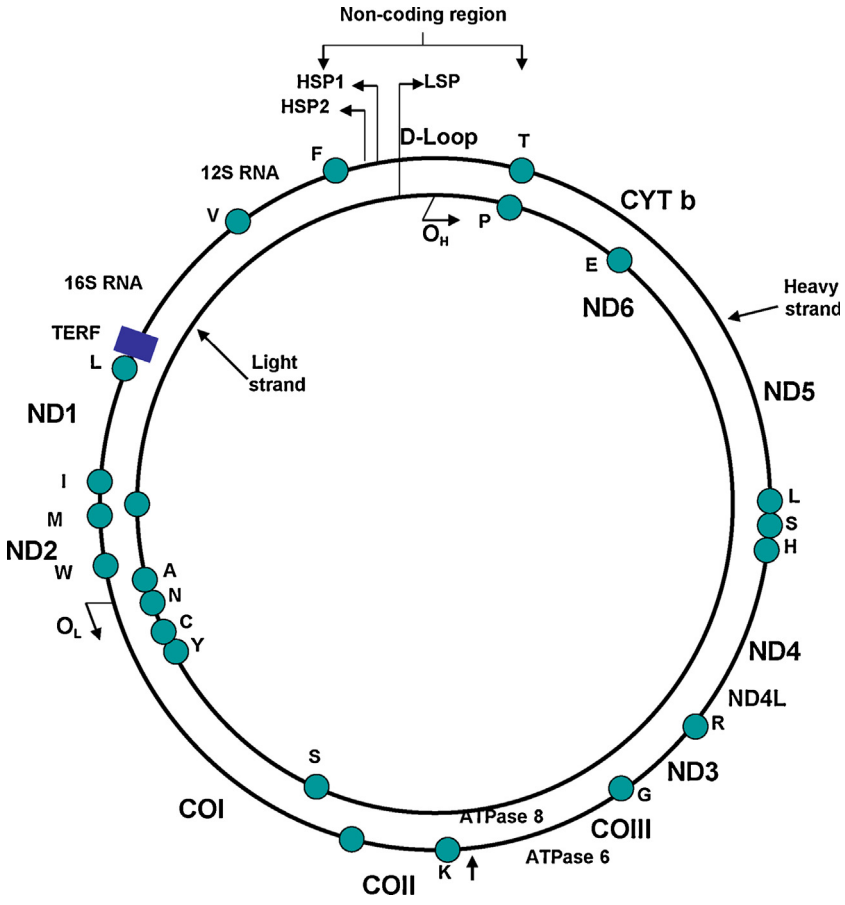

Fig. 1. Schematic diagram of the circular molecule of mitochondrial genome. The two strands are denoted the heavy (H) and light (L) strand due to their different buoyant densities. The D loop contains the promoters for transcription of the H and L strand (HSP and LSP) as well as the origin of replication of the leading strand of mtDNA (O_H). Displayed are the 13 subunits of respiratory chain (including 7 subunits of complex I represented as ND1, 2, 3, 4, 4L, 5 and 6; one subunit of complex III represented as cytochrome *b*, three subunits of cytochrome *c* oxidase represented as COX I, II and III, and two subunits of ATP synthase represented as ATP6 and ATP8 and 2 rRNA encoding genes (12S and 16S rRNA) and 22 tRNAs namely F, V, L1, I, M, W, D, K, G, R, H, S1, L2, T, P, E, S2, Y, C, N, A, Q represented as blue balls along with the non-coding region (D-loop). O_H and O_L refer to the origin of H-strand and L-strand replication, respectively.

thirteen essential polypeptides of the OXPHOS machinery and in addition also contains two rRNA and 22tRNA molecules used for maintenance and expression of mtDNA [1], mitochondrial protein synthesis [2], mitochondrial proteolysis [3], mitochondrial protein import [4], mitochondrial replication and or fusion [5,6], iron–sulphur cluster synthesis [7], and citric acid cycle metabolism and fatty acid oxidation [8]. The mitochondrial genome is able to replicate itself independently of nuclear DNA. It is located in the inner mitochondrial matrix in close proximity to inner membrane which is the site where reactive oxygen species (ROS) are constantly produced due to oxidative phosphorylation. Therefore, mtDNA is a prime target for oxidative damage leading to generation of mutations. The mitochondria in a typical mammalian cell contain hundreds of copies of mtDNA depending on energy requirement of that particular tissue. The two strands of mtDNA are denoted as heavy (H) and light (L) due to their differing base composition [1]. The mtDNA molecule is densely packed with genes and contains only one long non-coding region known as the displacement loop (D-loop) which contains promoters for the transcription of L (LSP) and H (HSP) strand and origin of replication of the H strand (O_H). Transcription from LSP provides primers for initiation of mtDNA replication at O_H. However, this mtDNA replication is often abortive and stops at the end of the D-loop thereby producing the triple-stranded D-loop structure containing nascent H-strand. Transcription of the circular mtDNA molecule produces 13 mRNA molecules that all encode oxidative phosphorylation components, and the RNAs needed for the mitochondrial translation machinery [1]. Mitochondria also contain their own ribosomes that are distinct from the cytoplasmic ones, as well as a variety of translation factors [2].

The mammalian mtDNA polymerase γ (Polγ) required for the mtDNA replication is heterotrimeric and consists of a single catalytic subunit (PolγA) and a two accessory subunit (PolγB) forming a dimer [9,10]. The twinkle helicase forms a hexamer that unwinds mtDNA in the 5′-3′ direction [11]. The PolγA subunit harbours a 3′-5′exonucleolytic proofreading activity in three domains that contains conserved aspartate residues. Knockin mice with severe reduction of the Polγ proofreading activity develop extensive amounts of mtDNA mutations that lead to premature ageing syndrome, thus demonstrating the in vivo importance of active proofreading during mtDNA replication [12].

Due to oxidative phosphorylation and generation of ROS, mitochondria are one of the main targets of oxidative damage that can lead to either point mutations or large scale deletions (Fig. 2). Point mutations can be classified as single nucleotide changes, insertions or deletions, however, not all lead to the development of diseases(s). The mitochondrial genome is highly polymorphic due to these mutations. As a consequence mitochondria within cells may vary from each other with respect to their mitochondrial genome profile. This cellular difference is known as mitochondrial DNA heteroplasmy and may be more prevalent in non-dividing tissues because selection processes against cells with defective

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