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Review

Genetic and biochemical intricacy shapes mitochondrial cytopathies

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ABSTRACT

The major progress made in the identification of the molecular bases of mitochondrial disease has revealed the huge diversity of their origin. Today up to 300 mutations were identified in the mitochondrial genome and about 200 nuclear genes are possibly mutated. In this review, we highlight a number of features specific to mitochondria which possibly participate in the complexity of these diseases. These features include both the complexity of mitochondrial genetics and the multiplicity of the roles ensured by the organelles in numerous aspects of cell life and death. This spectacular complexity presumably accounts for the present lack of an efficient therapy in the vast majority of cases.

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Introduction

Considering the crucial role of mitochondria in energy production and the implication of these organelles in major cell metabolic pathways, it seems intuitive that any significant mitochondrial dysfunction should be either lethal or at least bring quite severe developmental anomalies, particularly in the brain. Accordingly, fetal lethality is early seen upon genetic disruption of genes encoding key mitochondrial proteins in mammalian models. In the mouse, lethality due to mitochondrial defect occurs at about day 8.0 of embryogenesis

Abbreviations: Aif, apoptosis-inducing factor; AOX, alternative oxidase; α-KGDH, α-ketoglutarate dehydrogenase; mtDNA, mitochondrial DNA; Nd1, internal NADH dehydrogenase (*Saccharomyces cerevisiae*, mitochondrial); PG, propyl gallate; PGC1, peroxisome proliferator-activated receptor gamma coactivator 1; PGL, paraganglioma; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SDH, succinate dehydrogenase; tRNA, transfer RNA; TCAC, tricarboxylic acid cycle

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(E8.0; equivalent in humans to Carnegie stage 8; day 17–19) (Larsson and Rustin, 2001). Prior to this, anaerobic (glycolytic) metabolism is regarded as the essential source of ATP necessary for embryonic development (Baker and Ebert, 2013). After this point, a shift to aerobic (oxidative phosphorylation) metabolism favored by increased oxygen supply, the so-called fetal shift, would sustain the organogenesis taking place during fetal development and later on.

The actual frequency of very early fetal lethality originating from mitochondrial dysfunction is difficult to estimate in humans. Yet, we know that severe mitochondrial dysfunction from genetic origin, although relatively rare, can occur at various ages in humans (Munnich and Rustin, 2001). This presupposes either a successful passage through the fetal period despite defective mitochondria, or a delayed appearance of the mitochondrial dysfunction after early fetal life. Subjects of this review, the complexity of mitochondrial genetics and the multiplicity of the roles ensured by the organelles, might provide explanations or rational hypotheses for these surprising observations.

Mitochondrial DNA genetics

In mammals, about 1500 proteins are required to build and ensure the functioning of mitochondria (Lopez et al., 2000). More than 99% of these are encoded by nuclear DNA, being spread on the different chromosomes, including the X chromosome. However, mitochondria, as chloroplasts in plant, possess their own DNA (mtDNA) resulting in an unorthodox genetics (Larsson and Clayton, 1995). In humans, except for extremely rare aberrant cases, strict maternal inheritance of mtDNA is observed (Taylor et al., 2003). The mitochondria from sperm are tagged with ubiquitin for elimination after fecundation (Sato and Sato, 2013). Due to this complex genetics with both nuclear and mitochondrial genomes involved, transmission of mitochondrial traits, including pathological ones, will thus follow different types of inheritance possibly known in humans: autosomal, X-linked, or maternal inheritance (Zeviani et al., 1989).

The intron-less 37 genes harbored by the circular mtDNA (16,569 bp) in humans encode 13 subunits of the respiratory chain, 22 transfer RNAs and 2 ribosomal RNAs (Fig. 1) (Attardi et al., 1989). Each cell possesses a high number of mitochondria, constantly undergoing fusion and fission, and even more mitochondrial DNA molecules. Thus several hundreds of thousands of copies of mtDNA, contained in several tens of thousands of mitochondria, are found in human oocytes, albeit with significant disparities between oocytes from one woman (Fig. 2). The huge pool of mitochondria contained in the fertilized egg is then randomly distributed between daughter cells. Through the successive divisions, mtDNA is thus progressively reduced to a thousand or less, a number varying according to cell types. But even after this drastic reduction in the number of mtDNA molecules, there is still plenty of room for heterogeneity in the mtDNA population in each cell. Indeed, cells will easily withstand a low-noise of deleterious base changes in mitochondrial mtDNA and together with mtDNA polymorphisms transmit it to daughter cells. This is presumably due to the low selection pressure resulting from the occurrence of high number of mtDNA copies and the limited functional engagement of the mitochondrial oxidative metabolism under most conditions. Noticeably, most of the huge population of mitochondria of the oocytes is presumably at rest as indicated by the absence of well-formed cristae, folds in the inner membrane which carry the respiratory chain complexes. As a result, oocytes will tolerate mtDNA mutations that might be deleterious at later stages. Interestingly, an excess of mitochondrial capacity under non-stressing condition has been also reported in the skeletal muscle of mouse where mitochondrial function has been impaired by the double knockout of the gene encoding PGC1α and β (Rowe et al., 2013). Obviously, the variation of this over capacity according to tissues, cell types, conditions or age, may participate in the striking tissue expression and course observed in most patients with mitochondrial diseases.

Within the mtDNA population of a cell, base changes may be either harbored by all mtDNA molecules of a cell, a condition known as homoplasmy, or only found in a sub-population of these mtDNA molecules, a condition known as heteroplasmy. The tissue-specific level of heteroplasmy in terms of functional mtDNA (low content) has been shown to mirror tissue expression of disease in a number of patients (Ballana et al., 2008). Incidentally, mixing or segregation of mtDNA polymorphisms through the strict maternal transmission provides a

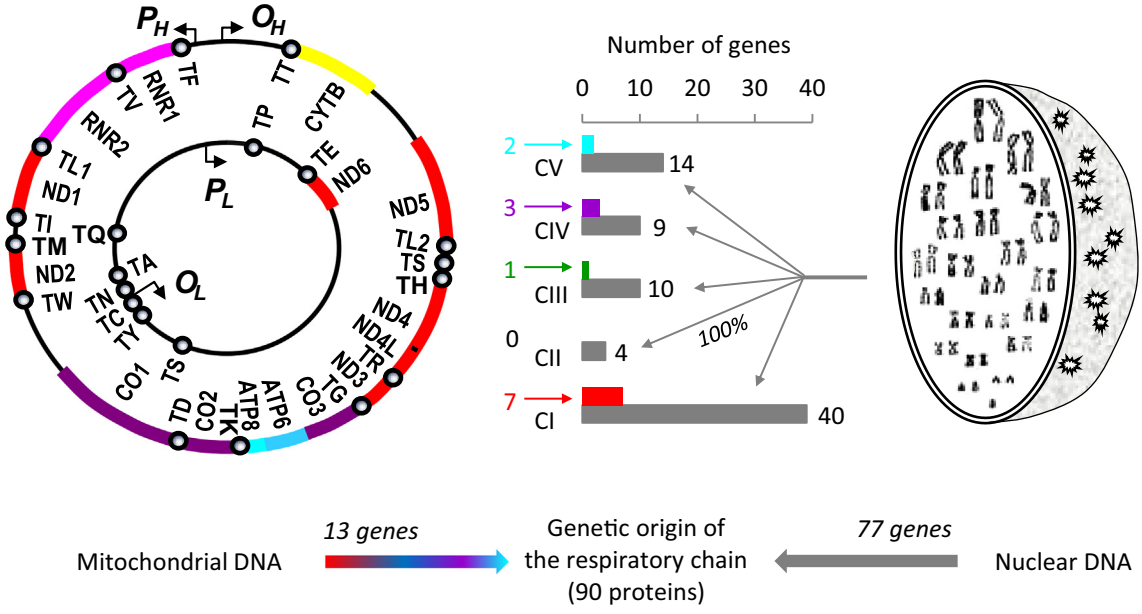

Fig. 1. Genes encoding mitochondrial respiratory chain subunits. The scheme shows the dual origin of the components of the respiratory chain encoded either by genes harbored by the mitochondrial DNA (left) or by genes distributed on the 46 (2 x 23) chromosomes of the nucleus (right). The medium graph specifies the nuclear (grey) or the mitochondrial (color) origin of the sub-units for each respiratory chain complex. Specifically, the four subunits constitutive of Complex II are all encoded by nuclear , *B, C*, and D. An identical color code is used for the scheme mapping the genes on the mitochondrial DNA. The displacement loop (D-loop) on the mitochondrial DNA map contains sequences that are used to initiate both mtDNA replication and transcription, including the L- and H-strand promoters (PL and PH, respectively) and the origin of H-strand replication (OH). The origin of light-strand replication is indicated (OL). Grey circles denote the different mitochondrial tRNAs harbored by the mitochondrial DNA.

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