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Energy

Mitochondrial cytopathies and the kidney

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ABSTRACT

Mitochondrial cytopathies include a heterogeneous group of diseases that are characterized by impaired oxidative phosphorylation. Current evidence suggests that renal involvement is probably more frequent than originally suspected but remains subclinical in a significant number of patients or is underestimated due to the severity of other clinical manifestations. Until recently, these diseases were thought to develop primarily in pediatric patients but patients that become symptomatic only in adulthood are now well recognized. From a renal standpoint, many patients with severe systemic disease and several patients with oligo-symptomatic clinical pictures have tubular defects, ranging from isolated tubular wasting of electrolytes to complete forms of renal Fanconi syndrome. Aside from rare cases of tubulo-interstitial and cystic diseases, other patients present with glomerular diseases that correspond in the majority of cases to focal segmental glomerulosclerosis lesions. Two specific entities should be singled out, namely the 3243 A>G mutation in the gene encoding for the mitochondrial leucine tRNA because it represents the most frequent form of mitochondrial glomerulopathy, and defects in the biosynthesis of coenzyme Q10 because they represent one of the few treatable forms of mitochondrial cytopathies.

1. Introduction

Mitochondrial cytopathies include a heterogeneous group of diseases that are characterized by impaired oxidative phosphorylation.

Typically, patients present with congenital or early onset symptoms, which, in the majority of cases, involve also the central nervous system [1]. Disease progression is characterized by worsening of the existing symptoms and by progressive involvement of additional organs or tissues, which appeared to be spared at earlier stages of the disease. In late stages, the central nervous system is nearly always involved. Beside the central nervous system and skeletal muscles, other organs that are frequently involved include heart, liver, the endocrine system (in particular pancreas and parathyroid glands), the hematopoietic system and the kidneys. Frequent manifestations include myopathy, encephalopathy, seizures, developmental delay, ophthalmoplegia, retinal degeneration, cardiomyopathy, diabetes mellitus, hypoparathyroidism and liver disease. Exercise intolerance is a frequent complain, particularly in adults with mild forms of diseases and is often dismissed as psychogenic or is misdiagnosed as chronic fatigue syndrome or fibromyalgia [2]. Some symptoms, such as sensorineural deafness or cardiomyopathy, can remain subclinical for many years and need to be screened systematically after the diagnosis of a mitochondrial disease. Patients may also present altered skin pigmentation or hair abnormalities [3].

2. Mitochondrial genetics

Mitochondria derive from ancient Gram-negative bacteria, which have adapted into an endosymbiotic process with eukaryotic cells more than 2 billion years ago [4]. During evolution, mitochondria have retained some key bacterial characteristics, including a double membrane and their own genome, i.e. the mitochondrial DNA (mtDNA). Vertebrate mitochondrial genome has its own genetic code, which is different from the "universal" genetic code, and structurally resembles prokaryotic DNA: it is circular, it is present in multiple copies within each mitochondrion, and genes lack introns. mtDNA is inherited solely from the mother while paternal mitochondria are rapidly degraded after fertilization [5]. Mitochondrial DNA encodes for 37 genes: 13 structural subunits of the respiratory chain and the 22 transfer RNAs and the

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2 ribosomal RNAs, which are required for mitochondrial protein synthesis [6]. Throughout the evolutionary process, an increasing number of mitochondrial proteins have become encoded by the genome of hosting cells, to the extent that the majority of functional and structural proteins that are required for mitochondrial biogenesis, maintenance and functions are encoded by nuclear genes. Therefore, mitochondrial diseases involving nuclear genes are inherited following classic Mendelian rules whereas mutations involving mtDNA follow a maternal inheritance modality, in which both genders can be affected, but only females transmit mutations to their children.

A number of polymorphisms exist in the mtDNA and these are usually homoplastic, meaning that they affect every mitochondrial genome within a cell. Conversely and with only few exceptions, pathologic mutations of mtDNA are heteroplastic, meaning that wild type and mutant molecules coexist in variable proportions within the same cell [4]. This phenomenon exists because most homoplastic pathogenic mutations would be lethal; some residual respiratory chain activity is required for cell survival. Because of the heteroplasmy phenomenon, symptoms develop according to the proportion of mutant mtDNA molecules present in different tissues (“threshold effect”). Usually, more than 70% of mtDNA needs to be mutated before cell dysfunction become apparent [4]. Moreover, during each cell division, mutant and wild type mtDNA segregate randomly in daughter cells (“random drift”) [4]. Therefore, tissues with high cell turnover, such as the bone marrow, tend to be less affected because healthier cells are selected during ongoing mitotic events. Conversely, postmitotic cells, such as neurons or podocytes, are more likely to be damaged. The complexity of inheritance and transmission of mtDNA mutations explains a large part of the phenotypic variability of diseases caused by mutations in mtDNA. For example, the classic 3243 A>G mutation in the gene encoding for the mitochondrial leucine tRNA can cause myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS) or may remain silent until adulthood where it becomes clinically apparent, causing steroid-resistant nephrotic syndrome and/or diabetes and/or sensorineural deafness (see below).

A third group of genetic disorders of mitochondria involves nuclear genes that are necessary to maintain and replicate mtDNA; despite affecting mtDNA, these diseases are transmitted through a Mendelian modality and are characterized by progressive mtDNA depletion [7].

Taken singularly, mitochondrial mutations are rare, but their overall frequency is relatively high: it is estimated that at least 1:5000 individuals is affected by one such mutation [8].

Different classifications have been proposed based on clinical, biochemical and molecular phenotypes or genotypes. A large number of mutations in mtDNA have been reported to date and are collected in online databases (http://www.mitomap.org). As mentioned above, phenotypes can vary considerably and phenotypic overlaps exist between different mutations. However, specific phenotypes are predominantly observed with some mutations, allowing to recognize specific clinical entities [2]. Examples include Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentary degeneration, cerebellar ataxia, heart block), myoclonus epilepsy and ragged red fibers (MERRF), Leber hereditary optic neuropathy (LHON), MELAS (see above), Leigh disease (subacute necrotizing encephalomyopathy, ataxia, respiratory troubles with weak cry, deafness, blindness), chronic progressive external ophthalmoplegia (CPEO) or Alpers’ disease (progressive infantile poliodystrophy, hepatic failure). Likewise, from a renal standpoint, any mutation that compromises the normal functioning of the respiratory chain can compromise normal nephron physiology but certain mutations cause renal tubular disorders whereas other cause primarily glomerular diseases.

3. The mitochondrial respiratory chain

Mitochondria are involved in several cell processes, including lipid and amino acid metabolism, cell proliferation, cell apoptosis and cell differentiation. Unquestionably, however, generation of ATP through oxidative phosphorylation in the respiratory chain represents their most important function, which is altered in mitochondrial cytopathies and is incompatible with life if completely abolished. The respiratory chain is composed of five complexes and of two electron carriers, namely coenzyme Q10 and cytochrome *c*. High-energy electrons produced by the Krebs’ cycle reactions enter the respiratory chain allowing the reduction of molecular oxygen (O_2) into water (H_2O). The energy released during this process is used to pump protons across the inner membrane of the respiratory chain, which generates an electrochemical gradient enabling complex V (or ATP synthase) to generate ATP. Cytochrome *c* transfers electrons from complex III to complex IV while coenzyme Q10 shuttles electrons from complex I or complex II to complex III. To accomplish this, coenzyme Q10 switches form an oxidized form (ubiquinone) to a reduced form (ubiquinol) (Fig. 1). In addition to serving as an electron shuttle, coenzyme Q10 also acts as a potent antioxidant, a property that explains part of the pathophysiology of diseases secondary to coenzyme Q10 biosynthesis defects.

4. Biosynthesis of coenzyme Q10

The biosynthesis of coenzyme Q10 is particularly complex and involves, in yeast, at least 12 proteins (reviewed in ref. [9]). Coenzyme Q10 is present in the normal diet, but, unless supplemented at pharmacological doses, is not sufficient to supply mitochondria, which need to have their own *de novo* biosynthesis pathway. Each molecule is composed of a quinone ring and a polyisoprenoid tail that contains 6, 9 or 10 units in yeast, mice or humans, respectively (coenzymes Q6, Q9, or Q10) [10] (Fig. 1). In humans, the quinone group is derived from 4-hydroxybenzoate, which itself derives from the tyrosine metabolism within the cytosol; the isoprenoid tail is produced through the mevalonate

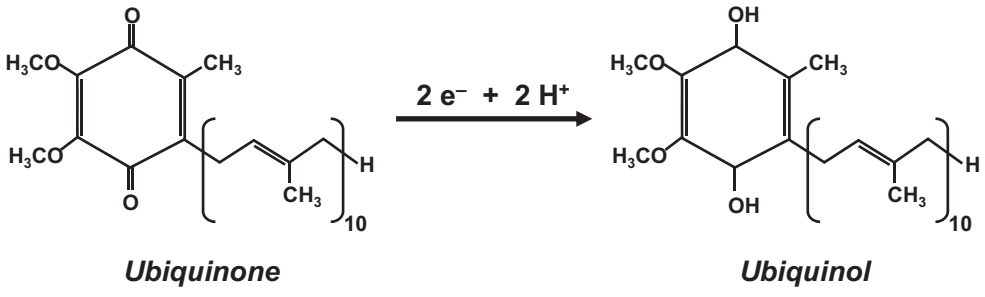

Fig. 1. Structure of coenzyme Q10 in its reduced (ubiquinol) and oxidized (ubiquinone) forms.