Preface

Coenzyme Q (CoQ) is a lipid-soluble redox molecule that is composed of a benzoquinone ring with a polyprenyl side chain: it is an essential electron carrier, it shows antioxidant properties, it regulates transition pores, and it is a specific substrate for both ETFDH of the β -oxidation of fatty acids and dihydroorotat dehydrogenase for pyrimidine nucleotide biosynthesis. CoQ biosynthesis depends on a pathway that involves at least ten genes (COQ genes), showing a high degree of conservation among species, and is carried out by a putative multi-subunit enzyme complex. The products of these genes comprise a very complex biosynthetic pathway, and their specific enzymatic and regulatory properties are beginning to be described [Bentinger et al., 2010]. CoQ deficiency impairs oxidative phosphorylation and causes clinically heterogeneous mitochondrial diseases (CoQ deficiency syndrome) that usually show severe and debilitating symptoms [Schon et al., 2010]. To date, mutations in 9 genes involved in CoQ biosynthesis (*PDSS1* and 2, *COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8/ADCK3*, *COQ9*, *ADCK4*) have been identified as primary causes of CoQ deficiency in humans. The clinical phenotype of CoQ deficient patients is diverse and includes (a) an encephalomyopathic form with muscle disorders and myoglobinuria, (b) an ataxic form with atrophic cerebellum, (c) a severe infantile

form with renal failure, (d) an isolated myopathy, and (e) nephrotic syndrome. The biological bases of the phenotypic differences between mutations in different COQ genes are still not known [Laredj et al., 2014]. Indeed, there are different conditions that induce secondary CoQ deficiency such as mtDNA depletion, mutations in either the DNA-repairing *aprataxin* or in the enzyme ETFDH of the β -oxidation of fatty acids pathway, recurrent food intolerance and allergies, methylmalonic aciduria, and myalgic encephalomyelitis/chronic fatigue syndrome. Understanding the molecular mechanism(s) leading to secondary deficiency is important to understand the highly regulated mitochondrial equilibrium, but it apparently depends on its role in the superassembly of respiratory complexes [Lapiente-Brun et al., 2013] and that all of these phenotypes are supported in somatic cells by a common survival transcriptome and an epigenome profile [Fernández-Ayala et al., 2013]. Several issues are still open to better understand this syndrome, including molecular diagnosis, genetic causes and therapy. The molecular diagnosis in patients is still problematic due to the involvement of a high number of genes, the absence of clear genotype/phenotype correlation, and the still unknown mechanism of CoQ biosynthesis and its regulation. The only therapeutic approach currently available

for CoQ deficiency syndrome is the supplementation of CoQ. While this approach is quite successful in some patients, with a clear improvement of the pathological phenotype, some patients do not respond. New therapeutic technologies would be necessary to improve mitochondrial functions that would involve both mitochondrial biogenesis and mitophagy.

This issue reflects the current view of CoQ biosynthesis and its major role in the respiratory chain. We summarize the clinic of these patients and the protocols for

both biochemical and genetic diagnosis. Alternative therapeutics are also discussed. Finally, the complexity of the syndrome requires new research approaches mainly by using animal and cellular models, which is also described.

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Plácido Navas

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