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Coenzyme Q biosynthesis in health and disease

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ABSTRACT

Coenzyme Q (CoQ, or ubiquinone) is a remarkable lipid that plays an essential role in mitochondria as an electron shuttle between complexes I and II of the respiratory chain, and complex III. It is also a cofactor of other dehydrogenases, a modulator of the permeability transition pore and an essential antioxidant.

CoQ is synthesized in mitochondria by a set of at least 12 proteins that form a multiprotein complex. The exact composition of this complex is still unclear. Most of the genes involved in CoQ biosynthesis (*COQ* genes) have been studied in yeast and have mammalian orthologues. Some of them encode enzymes involved in the modification of the quinone ring of CoQ, but for others the precise function is unknown. Two genes appear to have a regulatory role: *COQ8* (and its human counterparts *ADCK3* and *ADCK4*) encodes a putative kinase, while *PTC7* encodes a phosphatase required for the activation of Coq7.

Mutations in human *COQ* genes cause primary CoQ_{10} deficiency, a clinically heterogeneous mitochondrial disorder with onset from birth to the seventh decade, and with clinical manifestation ranging from fatal multisystem disorders, to isolated encephalopathy or nephropathy.

The pathogenesis of CoQ_{10} deficiency involves deficient ATP production and excessive ROS formation, but possibly other aspects of CoQ_{10} function are implicated.

CoQ_{10} deficiency is unique among mitochondrial disorders since an effective treatment is available. Many patients respond to oral CoQ_{10} supplementation. Nevertheless, treatment is still problematic because of the low bioavailability of the compound, and novel pharmacological approaches are currently being investigated.

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1. Coenzyme Q

Coenzyme Q (CoQ or simply Q) is a lipophilic molecule ubiquitously present in cell membranes, but especially abundant in mitochondria [1]. It is comprised of a quinone group and of a polyisoprenoid tail of variable length in different species: yeast have six units (CoQ_6), mice nine (CoQ_9) and humans ten (CoQ_{10}).

The ability of this peculiar molecule to sustain continuous oxidation–reduction cycles makes it an excellent membrane antioxidant [2,3] and an electron carrier in many crucial cellular pathways [4]. In the respiratory chain it transfers electrons from NADH: coenzyme Q reductase (complex I) and succinate: coenzyme Q reductase (complex II) to coenzyme Q: cytochrome c reductase (complex III). But it also serves as an electron acceptor for glycerol-3-phosphate, dihydroorotate, choline, sarcosine, sulfide, and several amino acid and fatty acylCoA dehydrogenases [5,6]. Finally, it constitutes an essential cofactor of uncoupling proteins [7], and a modulator of the mitochondrial permeability transition pore [8].

The interest of medical researchers for this biochemical pathway is related to the fact that CoQ_{10} deficiency has been observed in patients. It was first described in 1989 but only in the last decade the molecular bases of this disorder have been elucidated [9]. Patients with this biochemical phenotype may be classified in two groups, those with primary deficiency harbour mutations in one of the genes involved in the biosynthesis of CoQ_{10} (see below) while with secondary deficiency is associated to mutations in genes unrelated to the CoQ_{10} biosynthetic pathway or to non-genetic causes. In this review we will discuss the CoQ biosynthetic pathway, its regulation, and its alterations in primary CoQ_{10} deficiency.

2. CoQ biosynthesis

The biochemical pathway responsible for CoQ biosynthesis is still incompletely characterized. *Saccharomyces cerevisiae* is able to use either *para*-aminobenzoic acid (pABA) or 4-hydroxybenzoate (4HB) as a precursor of CoQ [10,11], while in mammals the precursor of the quinone ring is only 4HB, which is derived from tyrosine through an

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uncharacterized set of reactions. The isoprenoid tail is synthesized through the mevalonate pathway, which is common also to cholesterol biosynthesis [12]. The mevalonate pathway comprises the reactions that starting from acetyl-CoA produce farnesyl pyrophosphate (FPP) (Fig. 1).

In eukaryotes the initial part of the mevalonate pathway involves the condensation of three acetyl-CoA to 3-hydroxy-3-methylglutaryl-coenzyme A by HMG-CoA reductase, the main regulatory enzyme in cholesterol biosynthesis. Mevalonate is subsequently phosphorylated in two steps by mevalonate kinase (MVK) and phosphomevalonate kinase. Then, decarboxylation of mevalonate pyrophosphate yields isopentenyl pyrophosphate (IPP), which is the precursor of FPP and also the building block for the biosynthesis of dolichol and the side chain of CoQ. Isomerization of IPP gives dimethylallyl pyrophosphate, and FPP-synthase utilizes IPP and dimethylallyl pyrophosphate to make FPP with the intermediary formation of geranyl pyrophosphate (GPP). FPP is converted in cholesterol, dolichols, CoQ or used to farnesylate proteins, through squalene synthase, *cis*-prenyltransferase, *trans*-prenyltransferase, or farnesyl-protein transferase. Remarkably, HMG-CoA reductase, that converts HMG-CoA to mevalonate, is inhibited by statins, a class of compounds — widely used for the treatment of hypercholesterolemia.

The terminal steps in CoQ biosynthesis are thought to be rate limiting for the process in eukaryotes and take place in the mitochondrial matrix (Fig. 1). In yeast they involve at least 12 proteins (see Table 1) encoded by *COQ* genes [13,14].

The polyisoprenoid chain is synthesized by Coq1, and its length, depending on the species, may range from 6 (CoQ_6) to 10 (CoQ_{10}) isoprene units. This isoprene product is then condensed to a benzoquinone ring by Coq2 [15]; while Coq3, Coq5, Coq6, and Coq7 are involved in methylation, decarboxylation, hydroxylation and deamination reactions [16–19]; Yah1p and Arh1p provide electrons for Coq6 activity [10]. Coq8 is an atypical protein kinase essential for phosphorylation of Coq3, Coq5 and Coq7 [20]. Its human orthologue, ADCK3, has ATPase activity and its structure reveals a protein-kinase like fold and adenine nucleotides binding motifs [21,22]. Coq9 is a lipid-binding protein necessary to stabilize Coq7 and apparently controls the deamination

Table 1
Genes involved in CoQ biosynthesis in yeast and mammalian cells.

S. cerevisiae	*Homo sapiens*	Function
Enzymes		
COQ1	***PDSS1***	Prenyl diphosphate synthase
	PDSS2	
COQ2	***COQ2***	Prenyltransferase
COQ3	*COQ3*	O-methyltransferase
COQ5	*COQ5*	C-methyltransferase
COQ6	***COQ6***	Mono-oxygenase
COQ7	***COQ7***	Hydroxylase
YAH1	*FDX1L*	Electron transfer to COQ6
ARH1	*FDXR*	Electron transfer to COQ6
Non-enzymatic role		
COQ4	***COQ4***	Stabilization of Q complex
COQ8	***ADCK3***	Putative kinase. Phosphorylation
	ADCK4	of other Coq proteins ?
COQ9	***COQ9***	Lipid-binding protein. Co-factor of COQ7?
COQ11	?	Decarboxylase ?
Chaperone/transporter		
COQ10	*COQ10A*	Necessary for correct localization
	COQ10B	of CoQ within inner mitochondrial membrane
Role in CoQ biosynthesis postulated but not yet demonstrated		?
MCP2	*ADCK1*	?
?	*ADCK5*	
YPL109c	*ADCK2*	?

Genes in bold have been associated to primary CoQ_{10} deficiency in human patients.

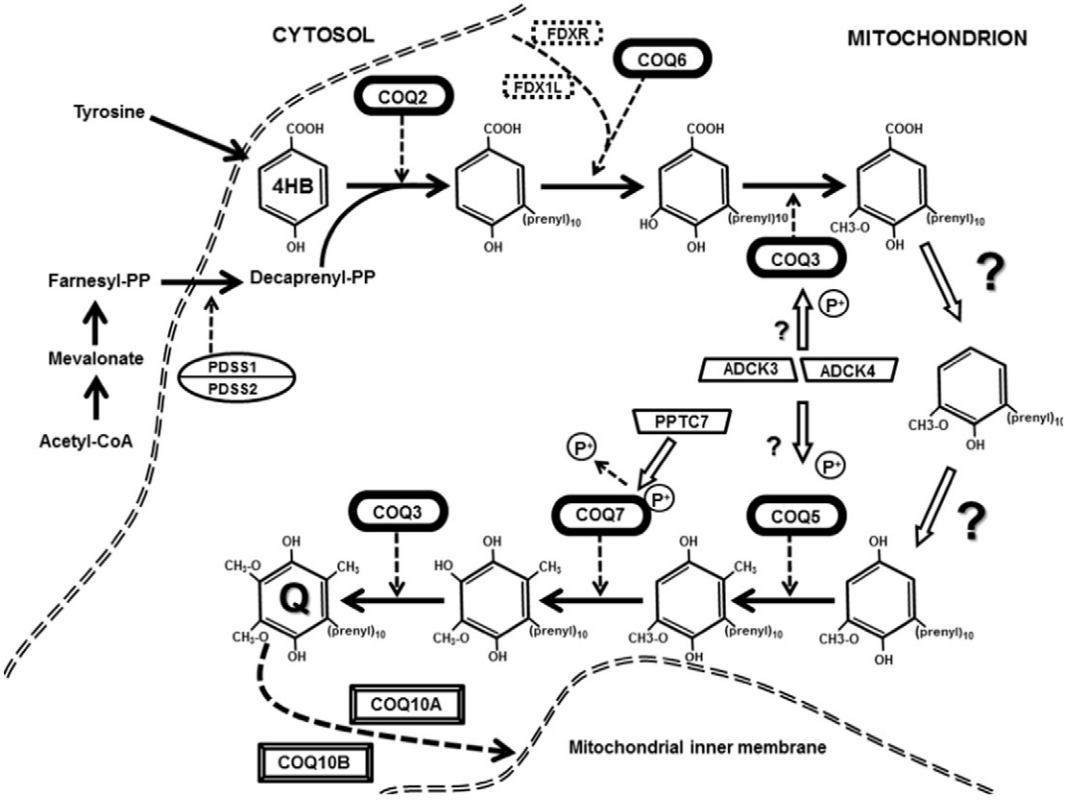

Fig. 1. The coenzyme Q biosynthetic pathway in mammalian cells. The question marks indicate the still uncharacterized enzymatic steps.

of CoQ intermediates that derive from pABA [18,23]. Coq10 is a START polypeptide that binds CoQ and facilitates both *de novo* CoQ biosynthesis and respiratory electron transport probably directing the localization of CoQ within the mitochondrial membrane [24]. Finally, Coq11 appears to be necessary for *de novo* CoQ synthesis in yeast, with a predicted role as a FMN-dependent decarboxylase [14] but it has no clear human orthologue. The function of Coq4 is still unknown, but there is evidence that it is required for the assembly and stability of the CoQ biosynthetic complex [25].

Yeast has been the principal model for the study of CoQ biosynthetic pathway, but all *COQ* genes have mammalian homologues (with the possible exception of *COQ11*), some more than one: *COQ8*, *COQ10* and *COQ*1 have two human orthologues each (*ADCK3* and *ADCK4*, *COQ10A* and *COQ10B*, and *PDSS1* and *PDSS2*). *ADCK1*, *ADCK2*, and *ADCK5* have been postulated to participate in the biosynthetic process but there still is no experimental proof of their involvement. Noteworthy, the function of *COQ2*, *COQ3*, *COQ4*, *COQ6*, *COQ7*, *ADCK3*, *ADCK4*, *COQ10A*, and *COQ10B* seems conserved in humans, because the human genes are able to functionally complement the corresponding yeast deletion mutants when growth in non-fermentable carbon sources [], Salviati, unpublished].

Yet, the enzymes that catalyse two steps of the ring modification (see Fig. 1), and virtually all the steps that lead to the production of 4HB from tyrosine are still unidentified.

3. CoQ complex organization

In yeast Coq1 to Coq9 polypeptides are localized to the mitochondrial matrix associated to the inner mitochondrial membrane [16,27] and in mammals we observed a mitochondrial localization for most of their orthologues (Desbats et al., unpublished). Coq proteins in yeast assemble in a multi-subunit complex, which is destabilized by the absence of a single Coq polypeptide [27]. The instability of several Coq proteins in Coq deletion mutants can be corrected through overexpression of the Coq8 kinase [28] or by supplementing the growth medium with CoQ_6 [26]. However, over-expression of Coq8 in the absence of Coq4, does not restore the formation of a high molecular mass complex necessary for CoQ biosynthesis, and 3-hexaprenyl-4-amino-5-hydroxybenzoic acid is the only CoQ-intermediate detected [26], indicating that Coq4 is essential for the stability of the CoQ biosynthetic complex.

The majority of co-complexed proteins retained their interactions from yeast to human, so we expect the CoQ complex to be conserved in mammalian cells [30,31]. This is supported by few experimental evidence showing that ADCK4 interacts with COQ6 and COQ7 in human podocytes [30] and steady-state levels of several Coq proteins were specifically decreased in hearts of mice harbouring the homozygous nonsense Coq9 R239X mutation [23].

The "CoQ-synthome model" based on co-IP, Gel Filtration Chromatography and Blue Native PAGE experiments, was proposed by Clarke and co-workers and predicts that a homodimer of Coq4 forms a scaffold through which Coq3, Coq5, Coq6, Coq7, and Coq9 associate to the CoQ complex [26]. Moreover, Ocaña and colleagues have proposed a two-step model for the organization of yeast CoQ complex: the formation of a pre-complex of 700 kDa containing most of the Coq proteins (with the exception of Coq7), which accumulates demetoxy-CoQ_6 (DMQ); and the mature CoQ complex assembly, of above 1 MDa (after the addition of Coq7) that produces CoQ_6 [31]. This model is based on the accumulation of DMQ in yeast grown in glucose medium and the conversion to CoQ_6 after post-diauxic-shift (PDS) or glycerol growth [32]. However most Blue Native experiments for Coq proteins reported so far identified several mitochondrial complexes with the most represented one being around 1 MDa; revealing the coexistence of different CoQ subcomplexes [29,33,34,26,27]. In addition, most Coq proteins in the *COQ7* deleted strain showed some instability [33]; CoQ complexes are absent in Δ*COQ7* strains which accumulate only the early intermediates 3-hexaprenyl-4-aminobenzoic acid and 3-hexaprenyl-4-hydroxybenzoic acid [26].

Fig. 2 depicts the putative structure of the complex.

The CoQ complex is probably composed of constitutively and dynamically expressed Q polypeptides to regulate its assembly under certain metabolic conditions. In fact, it was demonstrated the induction of expression of *COQ3*, *COQ4*, *COQ5*, *COQ7*, and *COQ8* after metabolic shift from fermentation to respiration [35]. Probably some subunits are pre-synthesized and pre-assembled, while others form part of the Q complex only temporally. In this scenario, the redox state of CoQ could function as a signal for Q complex regulation. However, the stability and turnover of Q complex subunits, its assembly pathway and stoichiometry are still unknown.

4. Regulation of CoQ biosynthesis

Despite the advances in the understanding of the CoQ biosynthetic pathway, there are still few data concerning its regulation. Preliminary studies in model organism like *Escherichia coli*, *S. cerevisiae* or *Saccharomyces pombe*, suggest that phosphorylation and dephosphorylation of Coq proteins represent key events in the modulation of CoQ biosynthesis [31]. The discovery of the putative kinase Coq8 in yeast, and its homologue UbiB in *E. coli* further supports this notion.

Generally, the lack of one of the Coq proteins (Δ*COQ* strains) leads to accumulation of the same intermediate in the CoQ_6 biosynthesis pathway in yeast. The over-expression of *COQ8* in the Δ*COQ8* strains has been shown to restore steady state levels of several Coq polypeptides and the accumulation of several CoQ_6 biosynthetic intermediates [28]. Coq8 has been described as an essential kinase for the phosphorylation of other Coq proteins. In particular, it has been demonstrated that Coq3, Coq5 and Coq7 are phosphorylated in a Coq8 dependent manner [20].

COQ8 displays a significant similarity with the human *ADCK3* and *ADCK4* that could be considered as its orthologue genes. The three proteins differ in the N-terminus, ADCK3 has a longer sequence which does not display the characteristics of the typical mitochondrial targeting sequences. ADCK3 and ADCK4 belong to a family of atypical kinases which includes (in mammals) five members ADCK1–ADCK5, all of them predicted as putative "atypical kinases" [36]. Despite the fact that they have been related to CoQ_{10} biosynthesis, a clear role has been demonstrated only for two of them. In fact, mutations in *ADCK3* and *ADCK4* have been associated with CoQ_{10} deficiency in humans [37,38,39,30]. It has also been shown that the ADCK4 protein interacts with COQ6 and COQ7 by co-immunoprecipitation studies in cultured human podocytes [30]. ADCKs proteins display an atypical protein kinase-like fold with multiple specific features, such as an alanine-rich loop replacing the canonical glycine-rich loop, or a long N-terminal extension that includes a conserved KxGC motif. Mutations of these specific features in *ADCK3* enable autophosphorylation and inhibition of CoQ biosynthesis *in vivo* [22]. The expression of *ADCK3* bearing the mitochondrial leader sequencing of either Coq3 or Coq8 in Δ*Coq8* yeast strains partially recovers the CoQ biosynthesis and the growth in glycerol medium. The phosphorylation state of Coq3, Coq5 and Coq7 is also partially restored by the expression of *ADCK3* [20].

Given the peculiar structure of Coq8 (and of ADCK3 and ADCK4) it is not yet clear if they are indeed kinases or if they simply recruit (and regulate) some other kinase(s) to the CoQ complex.

COQ3, a S-adenosylmethionine-dependent methyltransferase, catalyses the two O-methylation steps in CoQ biosynthesis. Previous studies in yeast have demonstrated that the phosphorylation state of Coq3 is directly implicated with the formation of the CoQ complex. Furthermore, Coq3 phosphorylation is Coq8 dependent, suggesting a regulatory function of Coq8 in the multi-subunit CoQ-biosynthetic complex formation [34,40,20].

COQ5 is a methyltransferase that catalyses the only C-methylation step observed in CoQ synthesis. Immunoprecipitation studies have shown that human COQ5 is associated with COQ4 indicating that both

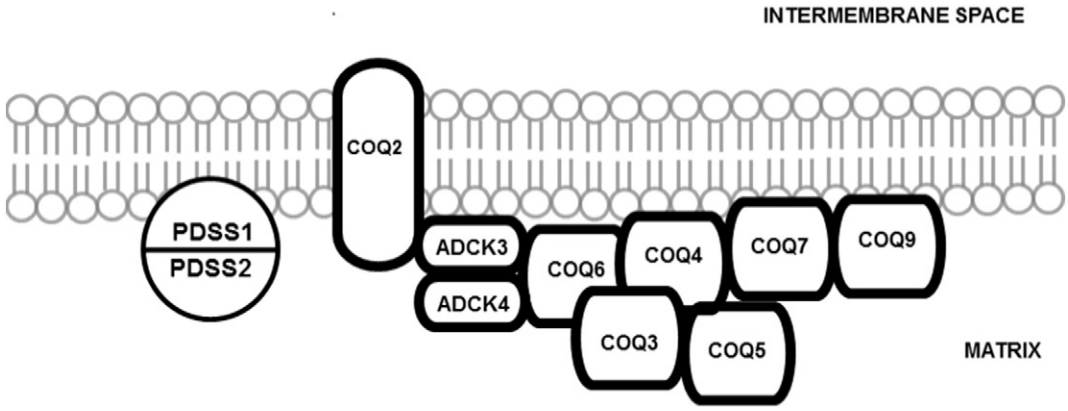

Fig. 2. Putative structure of the CoQ Complex in mammalian cells. The PDSS1–PDSS2 heterotetramer is probably not part of the complex.

are physically associated [29]. In addition, it has been shown that COQ4 co-migrates with COQ9 in a high molecular mass complex in humans [29]. Kanshin et al. [41], in a high throughput study, defined Coq5 as a phosphoprotein, whose phosphorylated active form depends on the presence of Coq8 kinase motifs [42,18].

The Ptc7 phosphatase seems to be another key regulatory element of coenzyme Q biosynthesis. While Coq3 and Coq5 phosphorylation may be necessary for complex assembly, there is evidence that phosphorylation could negatively regulate Coq7 [42]. Coq7 is a flavin-dependent monooxygenase that catalyses the hydroxylation of DMQ, the last monooxygenase step in CoQ synthesis. It was proposed that at least four residues of the Coq7 sequence are subjected to phosphorylation in a dependent manner of Coq8 kinase activity [20,43]. Martín-Montalvo et al. [42] have shown that Coq7 is phosphorylated in yeast under fermentative conditions, while become dephosphorylated when respiratory metabolism is induced. In this way, DMQ accumulates during fermentation and Coq7 activation through dephosphorylation by Ptc7 phosphatase allows CoQ production when respiration is needed [44]. Ptc7 is a mitochondrial Ser/Thr phosphatase that belongs to the Type 2 protein phosphatases group. The fact that Ptc7 expression is related with aerobic metabolism in yeast, as well as its direct role in Coq7 dephosphorylation suggest that the Ptc7/Coq7 system may be a regulator of CoQ synthesis [44]. The kinase phosphorylating Coq7 has not been identified yet.

Recently, new evidence of COQ9 role in the CoQ biosynthesis complex has been elucidated. The crystal structure of the human COQ9 has revealed a lipid-binding site while mass spectrometry analyses have demonstrated that purified COQ9 associates with coenzyme Q and other lipids. Moreover, Coq9 interacts physically and functionally with Coq7 in mice through conserved residues around the lipid-binding site [24]. Clarke and collaborators have also demonstrated that a *COQ5* point mutant with over-expression of *COQ8* accumulates nitrogen-containing intermediates when *COQ9* is deleted. Therefore, COQ9 seems to control the deamination steps in the biosynthesis pathway of the CoQ [18].

5. Primary coenzyme Q_{10} deficiency

CoQ_{10} deficiency can be defined as the presence of reduced levels of CoQ_{10} in tissues or cells of a patient. In practice, most diagnostic protocols rely on the analysis of skeletal muscle samples or cultured skin fibroblasts (while serum CoQ_{10} measurements are not useful for the diagnosis) [45]. As mentioned above, this biochemical finding may be a primary phenomenon due to mutations in *COQ* genes, or it may be secondary to defects in genes unrelated to CoQ_{10} biosynthesis. In this review we will focus on primary forms. Nevertheless, the existence of secondary forms (which are probably much more frequent than primary defects) is important because it demonstrates how the CoQ_{10} biosynthetic pathway can be easily perturbed.

Primary CoQ_{10} deficiency is a clinically and genetically heterogeneous disorder with age of onset ranging from birth to the 7th decade, and symptoms ranging from fatal neonatal multisystem disorder to isolated, adult-onset, encephalopathy or nephropathy [46]. To date mutations in nine of these genes have been identified (see Table 1). Many signs and symptoms reported in CoQ_{10}-deficient patients are common to other mitochondrial disorders, but some features such as steroid resistant nephrotic syndrome (SRNS) are typical of some forms of CoQ_{10} deficiency (see Table 2).

It is difficult to propose a comprehensive clinical classification, not only because of the marked clinical differences among different genes, but also because of the extremely wide spectrum of clinical manifestations among patients with mutations in individual genes. The case of *COQ2* defects is exemplary: phenotypes include a fatal neonatal multisystem disorder, a severe encephalomyopathy resembling Leigh syndrome, a MELAS-like encephalopathy associated with SRNS, isolated

Table 2
Renal and extrarenal manifestations of Coenzyme Q deficiency.

Tissue/organ	Manifestation	Gene defects
Kidney	SRNS	*PDSS1*, *PDSS2*, *COQ2*, *COQ6*, *ADCK4*
	Tubulopathy	*COQ9*
Central nervous system	Encephalomyopathy[a]	*PDSS2*, *COQ2*, *COQ4*, *COQ7*, *ADCK3*, *COQ9*
	Cerebellar ataxia	*PDSS2*, *COQ6*, *ADCK3*
	Leigh Syndrome	*PDSS2*, *COQ2*
	Stroke-like episodes	*PDSS2*, *COQ2*
	Seizures	*PDSS2*, *COQ2*, *COQ6*, *ADCK3*, *ADCK4*
	Dystonia	*ADCK3*
	Spasticity	*ADCK3*
	Migraine	*COQ2*
	Mental retardation[c]	*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *ADCK3*, *ADCK4*
Peripheral nervous system and sensory organs	Sensorineural deafness	*PDSS2*, *COQ2*, *COQ6*
	Optic atrophy	*PDSS1*, *COQ2*
	Retinitis pigmentosa	*PDSS2*, *COQ2*
	Peripheral neuropathy	*PDSS1*, *COQ4*
Muscle	Myopathy with lipid accumulation[b]	*COQ2*, *COQ4*
Heart	Hypertrophic cardiomyopathy	*COQ2*, *COQ4*
Liver	Liver failure	*COQ2*
Other	Lactic acidosis	*PDSS1*, *COQ2*, *COQ4*, *COQ7*, *COQ9*
	Dicarboxylic aciduria	*COQ2*

[a] Encephalomyopathy is a general term indicating severe brain and muscle dysfunction. No further details were provided in the original works.
[b] It does not include patients with a general diagnosis of "encephalomyopathy".
[c] Refers to patients surviving into childhood.

SRNS with onset in childhood or even in the second-third decade, and a late onset encephalopathy similar to multiple system atrophy [46]. The situation of *PDSS2* is similar. The reasons of these phenotypic diversities are not clear; however we have preliminary data that suggest that one of the main factors that determine the phenotype of *COQ2* patients is the residual activity of the mutant alleles. Instead, for *COQ9* mutations a key factor appears to be the different degree of impairment of formation of the Q complex [47].

We propose to classify the genetic defects of the CoQ_{10} biosynthetic pathway within three different groups.

A first group includes *PDSS1*, *PDSS2*, *COQ2*, *COQ6*, and *ADCK4*. These defects share common features and are associated with glomerular renal involvement manifesting as SRNS. SRNS is peculiar of CoQ_{10} deficiency, since it is rarely seen in other mitochondrial disorders (it has been reported only in few patients with the mtDNA 3243 A>G MELAS mutation), which usually present with tubular dysfunction [48]. SRNS may be an isolated finding or it may be associated with other neurological (or systemic) manifestations (Table 2). Patients with neonatal onset, severe forms, may not present with SRNS, or may develop it later on in the course of the disease.

A second group comprises *COQ4*, *COQ7*, and *COQ9*. These patients (even the milder cases or mouse models) never display SRNS, but the main clinical feature is encephalomyopathy. Other manifestations include hypertrophic cardiomyopathy, lactic acidosis, and (if renal involvement is present) tubulopathy [48–50].

The last group includes only *ADCK3* and the main clinical feature is cerebellar ataxia. Interestingly these patients have essentially central nervous system (CNS) involvement (other common symptoms are seizures, dystonia, cognitive impairment), but have virtually no other extra-CNS manifestations, despite a reduction of CoQ_{10} also in other tissues [37,51].

This classification has some limitations. For many genes, the reported number of patients is small (especially in the case of *COQ7* where a single kindred has been reported), therefore we cannot exclude that the phenotypic spectrum could be broader. Another point is that there is no clear explanation to the marked phenotypic differences among various gene defects, and there is no obvious common biological mechanism that characterizes each of the three groups. Tissue specific expression of individual genes (such as for example the case of *ADCK3* and *ADCK4*) cannot fully account for the differences in the clinical presentation. We suspect that additional roles in mitochondrial homeostasis (beyond CoQ_{10} biosynthesis) of some of the gene products could explain at least in part the clinical heterogeneity of defects of CoQ_{10} biosynthesis.

6. Pathogenesis of CoQ_{10} deficiency

The pathogenesis of CoQ_{10} deficiency involves two main aspects: reduced ATP production (in fact many of the features of this disorder are shared by other respiratory chain defects) and ROS production. However, there is evidence that the other physiological functions of CoQ_{10}, not directly linked to ATP synthesis, are involved in the pathogenesis of the disease. In fact silencing of *COQ6* in cultured podocytes results in increased apoptosis [52], while the growth phenotype of *COQ2*-mutant fibroblasts can be rescued by uridine, indicating that impairment of nucleotide metabolism (CoQ_{10} is required for the biosynthesis of pyrimidines) also plays a role in this disorder [53].

Interestingly, in cultured cells there appears to be an inverse relationship between the severity of CoQ_{10} deficiency, ATP defects, and ROS production. Severe CoQ_{10} deficiency is associated with marked decrease of cellular ATP content but no major increase in ROS, while relatively mild defects (30–50% residual CoQ) do not significantly impair ATP production but cause a significant increase of ROS production [54,55].

The role of ROS in the pathogenesis of glomerulopathy is supported by the observation that in the mouse model with *Pdss2* missense mutation, which presents essentially with isolated SRNS, CoQ_1 deficiency is ubiquitous, but a significant increase in ROS production is present only in the kidney, where tissue damage occurs [56]. However, quinone analogues such as idebenone, which are good antioxidants, but do not rescue mitochondrial respiration, are not effective in the treatment of this disease, indicating that both aspects (the bioenergetic defect and increased ROS production) are relevant for the pathogenesis of the disorder [57].

CoQ_{10} deficient cells also display increased autophagy. This appears a protective mechanism since inhibition of CoQ_{10} biosynthesis in cells that lack components of the autophagic pathway results in cell death [58]. However the precise role of autophagy is still controversial as recent data suggest that it could have a deleterious effect [59]. These authors also show that ER stress plays an important role and that it could represent an interesting therapeutic target.

7. Treatment of CoQ_{10} deficiency

The peculiarity of CoQ_{10} deficiency among mitochondrial disorder is that an effective treatment is available. In fact, many patients respond well to oral supplementation with high dose CoQ_{10}. CoQ_{10} supplementation can stop the progression of the encephalopathy [60] and of renal manifestations [61,48] in *COQ2*, *COQ6* and *ADCK4* patients. Data obtained in mice with *Pdss2* and *Coq9* mutations further support the efficacy of CoQ_{10} [62,63]. Conversely, quinone analogues such as idebenone, which are good antioxidants but do not rescue mitochondrial respiration, are not effective in the treatment of this condition [57,64]. It is essential to institute treatment as early as possible since once damage in critical organs (such as the kidney or the CNS) is established only minimal recovery is possible [60]. Two formulations of CoQ_{10} are currently available, ubiquinone (the oxidized form) and ubiquinol (the reduced form of CoQ_{10}). Most human data have been obtained with ubiquinone, but in mice ubiquinol seems to be more effective than ubiquinone, perhaps because of better bioavailability [63].

However, in patients with recessive *COQ4* or *ADCK3* mutations the clinical response is less striking if not absent [37,51, Salviati personal observation]. In part, this may be due to the fact that treatment is instituted once severe tissue damage has already occurred, but in many cases the reasons are not clear. Poor tissue delivery of CoQ (especially to CNS) has been invoked to explain therapeutic failures [63].

Recently novel approaches have been proposed. It has been shown that probucol, an antioxidant and hypolipidemic drug, has beneficial effects in *Pdss2* mutant mice [65], but no data on other genetic defects or human subjects are available. The exact mechanism of action of probucol is still under investigation.

It is also possible in case of some specific *COQ6*, *COQ7* mutants to bypass the enzymatic defect by providing the cells some modified analogues of 4HB the precursor of the quinone ring of CoQ_{10} [17]. This approach is effective only if the CoQ_{10} complex is assembled (*i.e.* with catalytically inactive but structurally stable mutants). Human *COQ6* mutant alleles are responsive to vanillic acid or 3,4-hydroxybenzoic acid [66], while 2,4-hydroxybenzoic acid has been successfully used in *COQ7* mutant fibroblasts [67]. This approach is particularly interesting because these compounds are not toxic, have good bioavailability, may cross the blood–brain-barrier, and restore endogenous CoQ_{10} production which is much better than providing exogenous CoQ_{10} [68].

Finally, supplementation with CoQ_{10} at birth has been proposed for sibling of patients with CoQ_{10} deficiency without a genetic diagnosis, pending the results of biochemical analyses [69].

Despite the progress in the understanding of CoQ_{10} biosynthesis, there are still many open issues that remain to be solved. The enzymes involved in several biosynthetic steps and the precise composition of the CoQ_{10} complex are still unknown, as well as the majority of the factors involved in the regulation of the pathway. The exact functions of the ADCK and COQ10 proteins, and of COQ4 remain to be elucidated. There is still no practical way to monitor therapy (although a recent

article provides an interesting solution to this issue, at least for patients without renal insufficiency, by measuring CoQ_{10} content in urinary sediment cells [70]) and the factors that influence the clinical response to CoQ_{10} supplementation are still largely unknown. Clarifying these points is one of the challenges in the research in the field of coenzyme Q for the next years.

Transparency Document

The transparency document associated with this article can be found, in online version.

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