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COMPLEX LIPIDS

Genetic bases and clinical manifestations of coenzyme Q_{10} (CoQ_{10}) deficiency

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Abstract Coenzyme Q_{10} is a remarkable lipid involved in many cellular processes such as energy production through the mitochondrial respiratory chain (RC), beta-oxidation of fatty acids, and pyrimidine biosynthesis, but it is also one of the main cellular antioxidants. Its biosynthesis is still incompletely characterized and requires at least 15 genes. Mutations in eight of them (*PDSS1, PDSS2, COQ2, COQ4, COQ6, ADCK3, ADCK4,* and *COQ9*) cause primary CoQ_{10} deficiency, a heterogeneous group of disorders with variable age of onset (from birth to the seventh decade) and associated clinical phenotypes, ranging from a fatal multisystem disease to isolated steroid resistant nephrotic syndrome (SRNS) or isolated central nervous system disease. The pathogenesis is complex and related to the different functions of CoQ_{10}. It involves defective ATP production and oxidative stress, but also an impairment of pyrimidine biosynthesis and increased apoptosis. CoQ_{10} deficiency can also be observed in patients with defects unrelated to CoQ_{10} biosynthesis, such as RC defects, multiple acyl-CoA dehydrogenase deficiency, and ataxia and oculomotor apraxia.

Patients with both primary and secondary deficiencies benefit from high-dose oral supplementation with CoQ_{10}. In primary forms treatment can stop the progression of both SRNS and encephalopathy, hence the critical importance of a prompt diagnosis. Treatment may be beneficial also for secondary forms, although with less striking results.

In this review we will focus on CoQ_{10} biosynthesis in humans, on the genetic defects and the specific clinical phenotypes associated with CoQ_{10} deficiency, and on the diagnostic strategies for these conditions.

Introduction

Coenzyme Q (CoQ, ubiquinone, or simply Q) is a remarkable lipid present in virtually all eukaryotic cells which is involved in many crucial cellular pathways (Crane and Navas 1997). It shuttles electrons from NADH:coenzyme Q reductase (complex I) and succinate:coenzyme Q reductase (complex II) to coenzyme Q:cytochrome *c* reductase (complex III) of the RC, it is an essential cofactor of uncoupling proteins (Echtay et al 2000) and of several mitochondrial dehydrogenases, among which dihydroorotate dehydrogenase (DHODH) which participates in pyrimidine biosynthesis and electron transfer flavoprotein dehydrogenase (ETFDH) involved in beta-oxidation of fatty acids (Fig. 1). It is also an important antioxidant (Ernster and Dallner 1995) and a modulator of the mitochondrial permeability transition pore (Fontaine et al 1998), thereby controlling apoptosis.

CoQ_{10} is highly relevant for clinicians because it has been implicated in many common disorders with increased oxidative stress such as neurodegenerative diseases, cancer, cardiovascular diseases, diabetes mellitus, aging, and Alzheimer's disease (Dhanasekaran and Ren 2005), however there is also a group of relatively more rare conditions characterized by a deficiency of CoQ_{10} in tissues. In this review we will focus on the genetic bases and the clinical phenotypes associated with primary and secondary CoQ_{10} deficiency.

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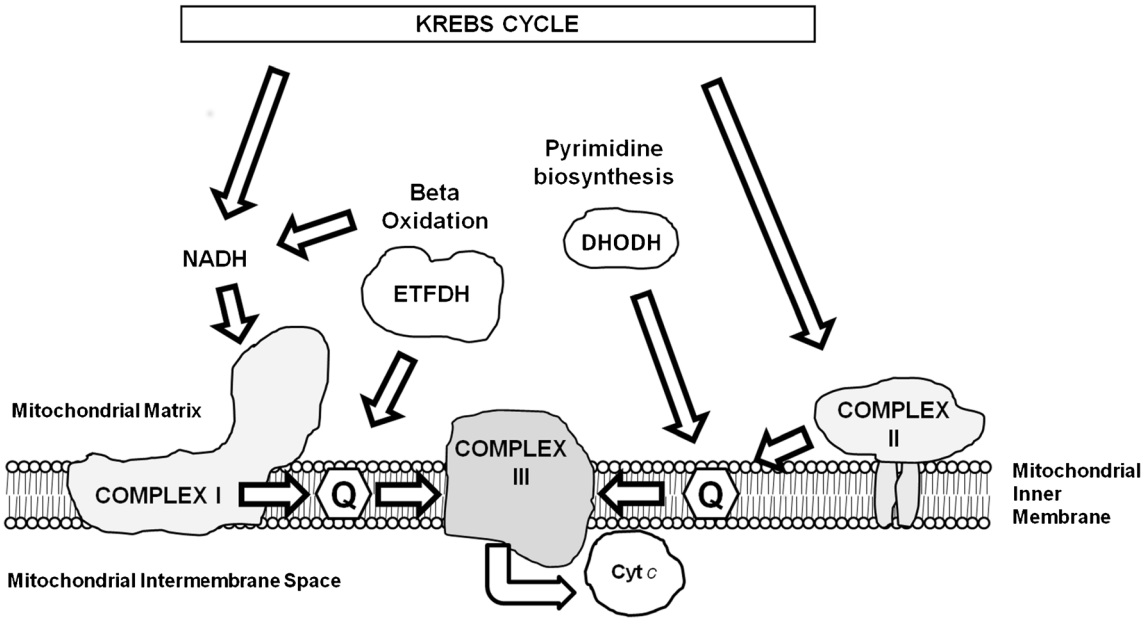

Fig. 1 The main roles of enzyme Q (Q) in mitochondrial metabolism. The *arrows* indicate electron flow through these pathways. ETFDH = electron transfer flavoprotein dehydrogenase, DHODH = dyhydroorotate dehydrogenase, Cyt *c* = cytochrome *c*

CoQ structure and biosynthesis

CoQ is composed of a quinone ring connected to a polyisoprenoid side chain of variable length: 10 isoprenic units in humans (CoQ_{10}), 9 in mice (CoQ_9) and 6 in yeast (CoQ_6) (Fig. 2). The CoQ biosynthetic pathway is complex and still incompletely characterized even in simple organisms. Yeast has been the principal model for the study of this pathway, which involves at least 12 proteins, encoded by COQ genes, all of which have mammalian homologues (Turunen et al 2004). In yeast Coq proteins assemble in a multi-subunit complex which requires the presence of all its components for its stability (Marbois et al 2005). This complex seems to be present also in mammalian cells (Ashraf et al 2013). However, the exact composition and organization of this complex is not completely clear yet.

The precursor of the quinone ring of CoQ is 4-hydroxybenzoate (4HB) which is derived from tyrosine through a still uncharacterized set of reactions, while the isoprenoid tail is synthesized through the mevalonate pathway which is common also to cholesterol biosynthesis. Yeast can also utilize para-aminobenzoic acid (pABA) in place of 4-hydroxybenzoic acid (4HB) (Marbois et al 2010), while in mammalian cells pABA acts as an inhibitor of CoQ biosynthesis. In eukaryotes the final steps of the biosynthesis, which are thought to be rate limiting, occur in mitochondria. The polyisoprenoid chain of the appropriate length is synthesized by Coq1p and then it is condensed to the benzoquinone ring by Coq2p (Forsgren et al 2004); Coq3p, Coq5p, Coq6p, and Coq7p are involved in methylation, decarboxylation, and hydroxylation reactions, while Yah1p and Arh1p provide electrons for Coq6p activity (Pierrel et al 2010). Coq8p is an atypical protein kinase essential for phosphorylation of Coq3p (Xie et al 2011) and possibly also of Coq5p and Coq7p. Overexpression of Coq8p can stabilize the multienzyme complex even in the absence of one of its components (Xie et al 2012). Coq10p is probably a chaperone required for the correct localization of CoQ within the mitochondrial membrane, although its precise function is still under scrutiny (Barros et al 2005). The functions of Coq4p and Coq9p are still unknown,

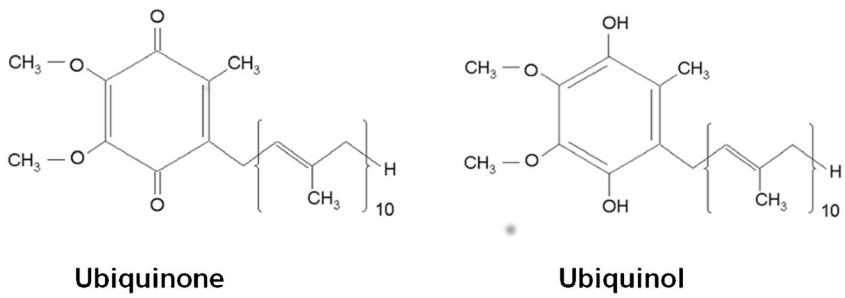

Fig. 2 Structure of the oxidized (ubiquinone) and reduced form (ubiquinol) of CoQ

but there is evidence that Coq4p is required for the formation and stability of the CoQ biosynthetic complex (Marbois et al 2009).

The biosynthetic pathway is highly conserved among species and several human COQ genes (*COQ2, COQ3, COQ4, COQ6, COQ7, ADCK3, ADCK4*, *COQ10A*, and *COQ10B*) can complement the corresponding yeast deletion mutants (Doimo et al 2014a, Salviati unpublished observations). Two yeast COQ genes have at least two human orthologues each (*ADCK3* and *ADCK4* for *COQ8*, and *COQ10A* and *COQ10B* for *COQ10*) whereas *COQ1*, which encodes a protein which forms a homotetramer, has two human homologues, *PDSS1* and *PDSS2*, which encode two proteins forming a heterotetramer. Moreover, there are three more genes (*ADCK1*, *ADCK2*, and *ADCK5*) which have been postulated to participate in the biosynthetic process but there is currently no experimental proof of their involvement (Table 1). Figure 3 depicts the biosynthetic process in human cells. It should be noted that several enzymes that catalyze specific enzymatic steps have not been characterized yet, even in lower organisms.

The exact subcellular localization of the biosynthetic reactions is still somehow debated. In yeast Coq1p to Coq9p polypeptides are localized to the mitochondrial matrix associated to the inner mitochondrial membrane (Tran and Clarke 2007) and in mammals we observed a mitochondrial localization for most of their orthologues (Desbats unpublished observations). However, in higher organisms CoQ is found in all cell membranes and its intracellular trafficking is still not understood. Extramitochondrial biosynthesis of CoQ has been postulated. It was demonstrated that UBIAD1, a nonmitochondrial prenyltransferase similar to COQ2, is localized in the Golgi membrane (Mugoni et al 2013), while immunofluorescence data (but not cell fractionation studies) suggested that human COQ6, besides mitochondria could also be present in the Golgi (Heeringa et al 2011). However, this issue remains highly controversial, especially because most mammalian COQ gene products do not display extramitochondrial localization and lack possible extramitochondrial homologues. Finally, very little is known about the regulation of the biosynthetic process in both higher and lower organisms.

Table 1 Genes involved in CoQ_{10} biosynthesis in humans and associated clinical phenotypes

Yeast gene	Human gene	Chromosomal location	Function	Reported patients (kindreds)	Nephrotic syndrome	Other clinical features
COQ1	*PDSS1*	10p12.1	Prenyl diphosphate synthase	2 (1)	N	Encephalopathy, peripheral neuropathy, optic atrophy, heart valvulopathy, mild lactic acidosis
	PDSS2	6q21		4 (2)	Y	Leigh syndrome, ataxia, deafness, retinopathy
COQ2	*COQ2*	4q21.23	4HB-prenyl transferase	14 (9)	Y	Encephalomyopathy, hypertrophyc cardiomyopathy, MELAS-like syndrome, seizures, retinopathy, lactic acidosis, deafness, adult-onset multisystem atrophy,
COQ3	*COQ3*	6q16.3	O-methyltransferase	–		
COQ4	*COQ4*	9q34.11	Organization of multienzyme complex	1	N	Encephalomyopathy
COQ5	*COQ5*	12q24.31	C-methyltransferase			
COQ6	*COQ6*	14q24.3	Mono-oxigenase (C5 hydroxylation)	11 (5)	Y	Deafness, encephalopathy, seizures
COQ7	*COQ7*	16p12.3	Hydroxylase (C6 hydroxylation)	–		
COQ8	*ADCK3*	1q42.13	Atypical kinase phosphorylation of COQ proteins	23 (14)	N	Cerebellar ataxia, encephalopathy, seizures, dystonia, spasticity
	ADCK4	19q13.2		15 (8)	Y	Mental retardation
COQ9	*COQ9*	16q21	?	1	N	Encephalomyopathy, renal tubulopathy, cardiac hypertrophy
COQ10	*COQ10A*	12q13.3	CoQ chaperone	–		
	COQ10B	2q33.1		–		
YAH1	*FDX1L*	19p13.2	Electron transfer to COQ6	–		
ARH1	*FDXR*	17q25.1	Electron transfer to COQ6	–		
ADCK1	*ADCK1*	14q24.3	?	–		
	ADCK5	8q24.3	?	–		
ADCK2	*ADCK2*	7q	?	–		

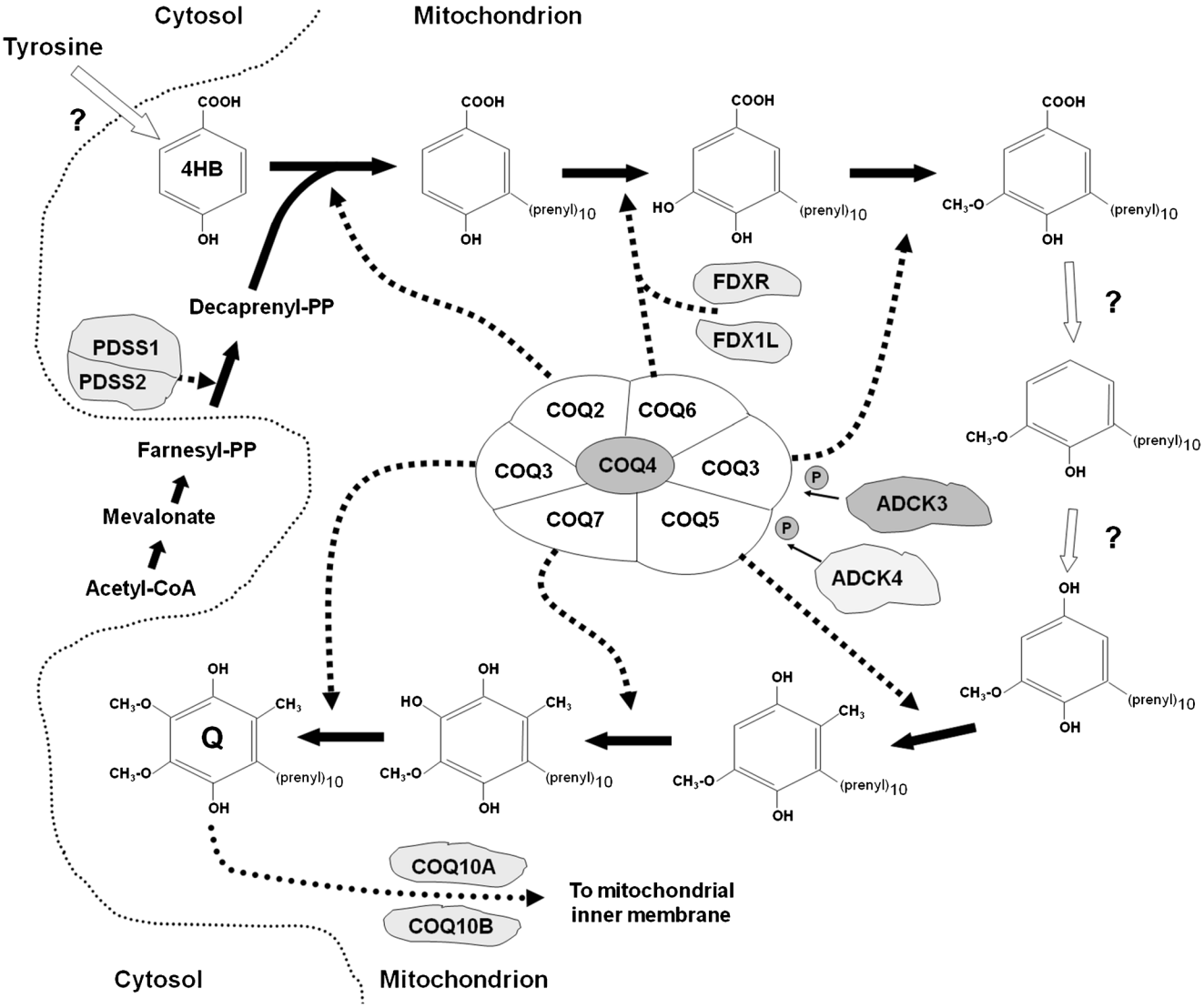

Fig. 3 Schematic representation of CoQ biosynthesis in mammalian cells. 4HB is derived from tyrosine through an uncharacterized set of reactions, while the lipidic portion is produced in the cytosol through the mevalonate pathway and in mitochondria by COQ1, which in mammals is a heterotetramer formed by PDSS1 and PDSS2 subunits. The other biosynthetic enzymes are grouped in a complex organized by COQ4. FDX1L and FDXR provide electrons to COQ6 but are also involved in other pathways. ADCK3 and ADCK4 appear to be associated to the complex but their precise role is unclear. Several enzymatic steps are still uncharacterized (*white arrows* and *question marks*). COQ10A and COQ10B appear to be necessary for the correct localization of CoQ within the mitochondrial inner membrane

CoQ deficiencies

CoQ_{10} deficiency is a biochemical finding first described in 1989 (Ogasahara et al 1989), which has been associated with a wide variety of clinical phenotypes. Most importantly, CoQ_{10}-deficient patients usually respond well to high dose CoQ_{10} supplementation, hence the necessity for clinicians to be familiar with these syndromes in order to perform a prompt diagnosis and to institute an appropriate treatment for patients.

The identification of the underlying genetic defects has allowed to distinguish primary forms, in which CoQ_{10} deficiency is caused by mutations in COQ genes, and secondary deficiency where the defect is associated to mutations in genes not directly related to the CoQ_{10} biosynthetic pathway (Trevisson et al 2011).

Primary deficiencies are very heterogeneous, both clinically and genetically, and are usually transmitted as autosomal recessive traits. To date, mutations in eight genes have been reported (*PDSS1,PDSS2, COQ2, COQ4, COQ6, ADCK3, ADCK4*, and *COQ9*) (Doimo et al 2014a) (Table 1). These conditions are very rare and, although there are no precise epidemiological data, we estimate their overall incidence in Italy to be inferior to 1:100,000. Traditionally, clinical manifestations have been clustered in five main phenotypes: encephalomyopathy, cerebellar ataxia, a severe infantile multisystemic form, nephropathy, and isolated myopathy

(Emmanuele et al 2012). Renal involvement consists of steroid resistant nephrotic syndrome (SRNS), a manifestation rarely found in other mitochondrial cytopathies, which instead is typical of CoQ_{10} deficiency (Emma et al 2012).

This classification is probably now outdated because the spectrum of clinical phenotypes observed in patients is much wider and includes other clinical manifestations such as cardiomyopathy, optic atrophy, and deafness, and many different combinations of symptoms have been identified (see below). Moreover, pure myopathy to date has never been documented in patients with genetically defined primary CoQ_{10} deficiency.

It should be noted that the majority of patients with a biochemical diagnosis of CoQ_{10} deficiency lack a definite genetic diagnosis and therefore it is not possible to classify them into primary or secondary forms. This holds true for most of the initial patients including the original two cases reported by Ogasahara (1989).

The clinical variability of CoQ_{10} deficiency concerns the age of onset (from birth to 7th decade) (Multiple-System Atrophy Research Collaboration 2013), the severity of the disease (from fatal multisystemic disorder to milder, tissue specific manifestations), the pattern of tissue involvement (even for patients with mutations in the same gene), and the clinical response to CoQ_{10} supplementation.

Clinical phenotypes associated with mutations in individual COQ genes

PDSS1

Only two siblings with *PDSS1* mutations have been reported: both were normal at birth, but then developed deafness, optic atrophy, overweight, macrocephaly, cardiac valvulopathy, and moderate pulmonary artery hypertension, mild mental retardation. Lactate in plasma was mildly elevated (Mollet et al 2007).

PDSS2

Two sibships were reported. The first case was a male infant, extremely hypotonic, who presented with seizures and vomiting, and cortical blindness. The MRI picture was compatible with Leigh syndrome and plasma lactate was elevated. CoQ_{10} supplementation was instituted but the child died at 8 months of age. The second family was originally described in 2000 (Rotig et al 2000), and it was later reported to harbor a *PDSS2* mutation. Three siblings had similar symptoms but with different severity. They presented visual impairment (bilateral visual loss with retinitis pigmentosa and optic nerve atrophy), bilateral sensorineural deafness, neurological impairment (ataxia, dystonia, amyotrophia), cardiomyopathy and nephrotic syndrome. The patient with the most severe manifestations died at age 8, while the one with the mildest could still walk unaided. CoQ_{10} therapy significantly improved their conditions (Rotig et al 2000; Rahman et al 2011).

COQ2

COQ2 was the first genetic defect to be associated with CoQ_{10} deficiency (Quinzii et al 2006). To date, COQ2 mutations have been identified in 14 patients from nine different families. Age of onset and clinical manifestations are extremely variable, and the genotype-phenotype correlations are still unclear. Clinical manifestations vary from isolated SRNS (Salviati et al 2005; McCarthy et al 2013; Diomedi-Camassei et al 2007), SNRS with encephalomyopathy resembling MELAS (Salviati et al 2005), to a rapidly fatal neonatal-onset multisystemic disease (Jakobs et al 2013; Mollet et al 2007). Although SNRS is frequent, it is not a constant feature and may develop only after other manifestations, such as hypertrophic cardiomyopathy (Scalais et al 2013; Dinwiddie et al 2013). Moreover, two patients presented in their 60s with an encephalopathy similar to multiple-system atrophy and retinopathy, without signs of renal involvement (The Multiple-System Atrophy Research Collaboration 2013). Oral supplementation of CoQ_{10} is usually effective for both neurological and renal manifestations (Montini et al 2008).

COQ4

COQ4 appears to be a crucial component of the biosynthetic pathway (Casarin et al 2008) and it is required to stabilize the multienzyme complex which catalyzes CoQ biosynthesis (Marbois et al 2009). To date only one patient with a defect in *COQ4* has been reported. He harbored a de novo 3.9 Mb deletion of chromosome 9q34 which included *COQ4*. Haploinsufficiency of COQ4 was associated to reduced CoQ_{10} biosynthesis and steady-state levels (approximately 50 % of controls) of CoQ_{10}. Besides facial dysmorphism and mental retardation, he displayed important weakness and hypotonia which improved significantly with CoQ_{10} supplementation. Attention also improved, while symptoms relapsed after inadvertent suspension of treatment (Salviati et al 2012). *COQ4* represents an exception because haploinsufficiency of other COQ genes does not affect CoQ levels, such as in Mclk1/Coq7 heterozygous mice (Lapointe and Hekimi 2008) or in carriers of *PDSS2* mutations (Salviati et al 2012). In this patient CoQ_{10} deficiency may be the precipitating event worsening the clinical picture caused by the haploinsufficiency of the other genes included in the deleted segment.

COQ6

Eleven patients from five families showed SRNS and extrarenal manifestations, such as sensorineural deafness,

ataxia, seizures, and white matter abnormalities. Two individuals displayed facial dysmorphism and five died in the early childhood. Treatment with oral CoQ_{10} decreased proteinuria, while hearing loss did not improve (Heeringa et al 2011).

ADCK3

ADCK3 mutations have been found in 23 patients from 14 families with autosomic-recessive progressive cerebellar ataxia (ARCA) (Lagier-Tourenne et al 2008; Anheim et al 2010; Gerards et al 2010; Mollet et al 2008; Terracciano et al 2012). Some of them had other manifestations, such as psychiatric disorders (Blumkin et al 2014), seizures, myoclonus, migraine or dysarthria. Childhood-onset is more common, but adult onset has also been reported (Horvath et al 2012; Liu et al 2014). Response to treatment is generally poor. Nevertheless, patients who responded well to treatment have been reported (Liu et al 2014).

ADCK4

ADCK4 is highly similar to *ADCK3*, but probably retains a different function because its mutations are associated with a completely different phenotype. *ADCK4* defects have been reported in 15 patients from eight families (Ashraf et al 2013). All displayed SNRS and only one had also neurological involvement. Seven underwent kidney transplant for reaching end stage kidney disease. Only one was treated with oral CoQ_{10} and responded well to treatment.

COQ9

Only one patient is reported. An older sister had died on day one of life for a multisystemic disorder with seizures and acidosis, but a diagnosis was not made. The patient first showed poor feeding and lactic acidosis, then he presented seizures and cerebral atrophy. Also, he developed cardiac hypertrophy and renal dysfunction. The patient died at 2 years of life (Duncan et al 2009; Rahman et al 2001).

The reason for the marked diversity in the clinical phenotypes associated with mutations in individual genes is unclear. Part of the variability could depend on the amount of residual biosynthesis (a complete block appears to be lethal, see Doimo et al (2014b)), but there are no extensive studies on the subject. The fact that the phenotype for *COQ6* and *ADCK4* mutations is more homogeneous than for *COQ2* probably reflects selection bias, since patients included in these studies were recruited from a cohort of individuals with SRNS as the principal clinical manifestation (Heeringa et al 2011; Ashraf et al 2013). In the case of *PDSS1* and *COQ4* single kindreds were reported, therefore the information is partial. Finally, the markedly different phenotype observed with mutations in genes like *ADCK3* (with exclusively CNS manifestations) could reflect the presence of compensatory mechanisms in selected tissues and/or the fact that this gene is involved in other processes besides CoQ biosynthesis.

Secondary deficiencies

While primary CoQ_{10} deficiencies are very rare, secondary forms are much more frequent. Patients present with CoQ_{10} deficiency (usually documented in skeletal muscle or cultured skin fibroblasts) but harbor defects in genes unrelated to CoQ_{10} biosynthesis.

Examples of secondary CoQ_{10} deficiency include mitochondrial myopathies (Sacconi et al 2010), and mitochondrial DNA depletion syndrome (Montero et al 2013), ataxia and oculomotor apraxia type I caused by mutations in aprataxin (*APTX*) (Quinzii et al 2005), glutaric aciduria type II or multiple acyl-CoA dehydrogenase deficiency (MADD), caused by mutations in *ETFDH* (Gempel et al 2007), cardiofaciocutaneous syndrome caused by mutations in *BRAF (*Aeby et al 2007), and methylmalonic aciduria (Haas et al 2009). CoQ_{10} deficiency has been reported also in non-genetic conditions such as fibromyalgia (Cordero et al 2009). The exact mechanisms by which these genetic defects cause CoQ_{10} deficiency are still unknown. Several hypotheses have been proposed, including interference with the signaling pathways regulating CoQ_{10} biosynthesis, alteration of the mitochondrial inner membrane milieu, interference with the formation of the CoQ_{10} biosynthetic complex, increased degradation of CoQ_{10} or a general impairment of mitochondrial function. In the case of MADD it has been shown that the mutant protein binds CoQ_{10} less tightly than the wild-type, suggesting oxygen can get access to the electrons in the misfolded mutant protein and generate superoxide and oxidative stress, which affect the CoQ_{10} pool (Cornelius et al 2013).

It is important to keep in mind that a reduction of CoQ_{10} levels is not a consistent feature in these conditions; in fact, it is present only in a minority of the patients harboring these defects. Why some individuals are particularly susceptible to develop CoQ_{10} deficiency is also unclear.

Specific symptoms in these patients depend on the underlying condition. However, most reports focus on skeletal muscle and the central nervous system (CNS). Muscular manifestations consist of weakness, hypotonia, exercise intolerance, myoglobinuria, while the main CNS manifestations include ataxia and general CNS impairment. Although in these situations CoQ_{10} deficiency is a secondary phenomenon, it probably exacerbates the symptoms caused by the primary molecular defect, and these patients often benefit from oral CoQ_{10} supplementation (Quinzii et al 2005), even though the response is not as dramatic as in those with the primary forms.

Several studies have reported a decrease in plasma CoQ_{10} concentration in diverse clinical conditions such as cardiomyopathies, degenerative muscle and central nervous system diseases, liver cirrhosis, and phenylketonuria (Bianchi et al 1994) (Turunen et al 2002) (Hargreaves 2007) (Littarru and Tiano 2010). The main limitation of these studies is that there is not a clear relationship between plasma and intracellular levels of $CoQ_{10,}$ therefore it is difficult to establish whether these findings reflect an actual CoQ_{10} deficiency in affected tissues.

Finally, there is much debate whether statin-induced myopathy is due to secondary CoQ_{10} deficiency. These compounds inhibit hydroxyl-methylglutaryl coenzyme A reductase, thus interfering not only with the biosynthesis of cholesterol, but also of CoQ_{10} (Deichmann et al 2010; Avis et al 2011). Nevertheless, there is no clear evidence that the patients with this condition actually develop CoQ_{10} deficiency in muscle, and there are insufficient data to support the use of CoQ_{10} supplementation in patients treated with statins (Trevisson et al 2011).

COQ variants genes as susceptibly factors for complex diseases

There is emerging evidence that polymorphic variants in COQ genes may contribute to development of specific multifactorial diseases. Polymorphic *COQ2* variants have been associated with an increased risk of developing multiple-system atrophy (Multiple-System Atrophy Research Collaboration 2013). However this finding has been recently challenged and further work is needed to clarify this issue (Jeon and Farrer 2014; Sharma et al 2014; Schottlaender et al 2014; Quinzii et al 2014). A specific *PDSS2* haplotype has been linked to SRNS with focal and segmental glomerulosclerosis (FSGS) in a large cohort of patients of European origin (Gasser et al 2013). Interestingly, lymphoblastoid cells of patients with FSGS displayed reduced CoQ_{10} levels independently of this haplotype indicating that reduced CoQ_{10} production by itself could predispose to FSGS.

Further studies are required to understand whether COQ gene variants could act as risk factors for other multifactorial diseases or act as modulator of the phenotype for other mendelian conditions.

Murine models

Currently, there are mouse models of primary CoQ deficiency presenting *Pdss2* and *Coq9* mutations. A naturally occurring mouse with homozygous missense *Pdss2* mutations recapitulates the nephropathy observed in patients. Interestingly CoQ_{10} supplementation is effective in this model in preventing development of renal manifestations (Saiki et al 2008). Although in these animals CoQ deficiency is widespread, there is a significant increase of ROS only in the kidney (Quinzii et al 2013). Mice with conditional *Pdss2* knockout in podocytes produces a similar nephropathy, while those with renal tubule-specific knockout did not develop the renal disease (Peng et al 2008). A cerebellum-specific KO mouse developed ataxia (Lu et al 2012), but response to treatment was not tested.

Finally, a constitutive *Coq9* Knockin (R239X) mouse model presents with encephalopathy (García-Corzo et al 2013) which appears to be responsive to treatment (García-Corzo et al 2014).

Pathophysiology of CoQ deficiency

Because CoQ_{10} is an essential component of the mitochondrial RC, its deficiency (regardless of whether it is a primary or secondary form) causes an impairment of the transport of electrons to complex III, and therefore an inhibition of oxidative phosphorylation and ATP production in cells (Quinzii et al 2008). In fact, symptoms in many cases resemble those of other mitochondrial cytopathies. However, the pathogenesis of CoQ_{10} deficiency is still incompletely understood and it is likely to also involve the other roles of CoQ unrelated to ATP production. The remarkable sensitivity of the glomerular podocytes to CoQ_{10} deficiency is especially puzzling, considering that most mitochondrial defects cause tubular, but not glomerular dysfunction. The antioxidant effect of CoQ_{10} is probably highly relevant, in fact renal involvement correlates with increased ROS production in this tissue (Quinzii et al 2013). Interestingly, there is an inverse relationship between the severity of CoQ_{10} deficiency in cultured fibroblasts and ROS production, such that even relatively mild defects (30–50 % residual CoQ_{10}) may still be harmful to the cell (Quinzii et al 2010).

Knockdown of *COQ6* resulted in increased apoptosis (Heeringa et al 2011), while knockdown of *ADCK4* caused decreased podocyte migration (Ashraf et al 2013) that could be rescued by CoQ_{10} supplementation. Interestingly, the impaired growth of CoQ_{10}-deficient fibroblasts could also be rescued by uridine (López-Martín et al 2007), indicating that abnormal nucleotide metabolism (CoQ is required for biosynthesis of pyrimidines) also plays a role in this disorder. Finally, CoQ_{10} deficiency promotes mitophagy in both primary and secondary defects (Rodríguez-Hernández et al 2009; Cotán et al 2011). In these cases mitophagy appears to be a protective mechanism because its block in CoQ deficient cells causes cell death (Rodríguez-Hernández et al 2009).

Diagnosis of CoQ_{10} deficiency

Diagnosis of CoQ_{10} deficiency usually involves a muscle biopsy, although most biochemical determinations can be carried out on cultured skin fibroblasts. Routine morphological studies on muscle sections do usually not yield specific findings. The histological picture may be normal while in severe cases there may be signs of mitochondrial proliferation. A common finding in both primary and secondary forms is the presence of lipid accumulation on Oil-Red stain (Trevisson et al 2011). Biochemically, there is a reduction of the enzymatic activities of RC NADH:cytochrome *c* reductase (complexes I+III) and succinate:cytochrome *c* reductase (complexes II+III), the two CoQ_{10}-dependent reactions, with normal activity of isolated complexes. The defect can be rescued in vitro by addition of decylubiquinone (a soluble CoQ analog) in the reaction cuvette (Salviati et al 2005) or by cultivating the cells in the presence of CoQ_{10}. These findings are highly suggestive of CoQ_{10} deficiency. Electron microscopy on renal biopsies generally shows numerous dysmorphic mitochondria in the cytoplasm of podocytes (Diomedi-Camassei et al 2007).

The definite biochemical diagnosis of CoQ_{10} deficiency is established by measuring CoQ_{10} content in skeletal muscle biopsies or cultured skin fibroblasts. It is possible to analyze also peripheral blood mononuclear cells (Duncan et al 2005). This approach is not invasive, however samples must be processed immediately and this represents a major limitation since CoQ_{10} determination is carried out only in a few selected laboratories, while muscle biopsies or cultured fibroblasts can be easily frozen and shipped to the diagnostic centers. A possible alternative are lymphoblastoid lines (Ashraf et al 2013). However, there is little experience with this approach, especially in secondary forms.

Most protocols rely on HPLC separation and electrochemical detection (Montero et al 2008) which yields more accurate results compared to the UV detectors used in the past. Plasma CoQ_{10} levels are not useful since they reflect the dietary intake of CoQ_{10} rather than endogenous production (Montero et al 2008).

It is also possible to measure CoQ_{10} biosynthetic rates in cultured fibroblasts. Traditional methods utilize radiolabeled substrates, but recently methods employing stable isotopes have been developed (Buján et al 2014). Although these techniques are not routinely employed for diagnosis they may be helpful in distinguishing primary from secondary forms.

Once a biochemical diagnosis is established, molecular genetic studies are performed. The large number of genes involved and the still incomplete characterization of the pathway make this a complex task. Next-generation sequencing technologies greatly simplify the analysis of panels comprising large numbers of genes; however, the high development cost of these panels, the relatively small number of patients with the primary forms, the incomplete knowledge of the pathway, and the dropping costs for whole exome sequencing (WES), make it an attractive alternative approach. In fact, WES may also explore all the possible causes of secondary forms (which may be hundreds considering just all possible causes of RC dysfunction).

Treatment of COQ deficiency

Oral supplementation with CoQ_{10} seems to be effective for a large number of patients, especially for those with primary deficiencies, but also for those with secondary forms. Renal, CNS, and muscular symptoms respond very well to treatment. However, it is important to note that treatment can stop the progression of the clinical manifestations but once severe kidney or CNS damage is established, it cannot be recovered (Montini et al 2008). In vitro models show that exogenous CoQ_{10} reaches the mitochondrial inner membrane where it reactivates electron flow within the RC (López-Martín et al 2007; López et al 2010). Interestingly the transcriptomic profile of deficient cells is also largely restored (Fernández-Ayala et al 2013).

Treatment consists of the administration of high doses of CoQ_{10}. Reported doses range from 5- mg/kg/day (Rotig et al 2000) to 30–50 mg/kg/day (Montini et al 2008), but in mice doses up to 200 mg/kg day have been employed (Saiki et al 2008). Because commercial preparations greatly differ in their characteristics, we advise to employ soluble forms, soft-gel caps or oily formulations, while tablets should not be used because of poor absorption (Bhagavan and Chopra 2007). The efficiency of absorption decreases with the increase of individual dose of CoQ_{10} therefore split doses should be preferred to single doses (Miles et al 2006). In our experience SRNS responded with 30 mg/kg/day, while for CNS manifestations lower dosages were sufficient. Response to treatment is usually evident in 10–20 days.

A good response is reported in most primary forms (either in patients or in mouse models) with the exception of *ADCK3* patients who usually do not respond to treatment. However, because even in this subgroup some responders have been reported (Liu et al 2014), a therapeutic trial with CoQ_{10} should also be warranted to these patients.

In the past only ubiquinone (the oxidized form of CoQ_{10}) was commercially available due to the difficulties to maintain the compound in the reduced form. Most data in patients has been obtained using ubiquinone. Recently, different solubilized and stabilized formulations that are able to preserve CoQ_{10} in its reduced form have been developed, and several companies are now marketing the reduced form ($CoQH_2$ or ubiquinol).

Both compounds are adsorbed from the GI tract and upon absorption ubiquinone is reduced to ubiquinol (Franke et al 2010) and then transported to peripheral cells bound to lipoproteins (Fig. 4).

Apparently ubiquinol is superior to ubiquinone (García-Corzo et al 2014), but experience in patients with primary forms is limited and there are no clear indications about the dose-equivalence of the two compounds.

Many different aspects may influence the variability of the clinical response to CoQ_{10} supplementation. Obvious factors are the therapeutic dosages, the pharmaceutical formulation employed, the severity of the underlying illness, and the progression of tissue damage (Trevisson et al 2011), but there are probably many other components, genetic, environmental, and even epigenetic (Fernández-Ayala et al 2013), that modulate the response to treatment. We stress the importance of providing adequate doses of CoQ_{10} and the appropriate formulations since often patients receive insufficient doses of the compound. It is also likely that the limited response seen in many of the patients with the neonatal onset forms (Doimo et al 2014a) is due to the fact that treatment was instituted when tissue damage (especially in the CNS) was already very advanced. The limited number of patients makes it hard to draw clear conclusions, and limits the possibility to perform clinical studies on this issue.

Other therapeutic options

Because of the low bioavailability of CoQ_{10}, other treatments have been investigated. Probucol, an antioxidant and hypolipidemic drug, is effective in *Pdss2*-mutant mice (Falk et al 2011). No data are available on humans, and it is not clear whether its action is exclusively related to the antioxidant effect or if it could have a stimulatory effect on residual CoQ biosynthesis. It should be noted that antioxidants such as idebenone, a short chain analogue of Q which does not restore electron flow in the RC (López et al 2010) are not effective in patients (Rotig et al 2000).

Reactivation of endogenous synthesis is a promising approach because endogenously produced CoQ_{10} will be delivered to the appropriate subcellular compartments, while with exogenous supplementation the distribution of CoQ_{10} is not controlled and it may have difficulties to efficiently reach mitochondria.

Drugs that stimulate the biogenesis of the mitochondrial RC and of other mitochondrial enzymes such as bezafibrate (BZF) have been proposed for other mitochondrial cytopathies (Wenz et al 2008), however we have no detected beneficial effects of BZF in CoQ_{10} deficient cells (Casarin et al 2012).

In the case of *COQ6* mutations, it is possible to bypass the enzymatic defect, by providing the cells with 4HB hydroxylated analogues such as vanillic acid (a commonly used flavoring agent). This approach was demonstrated in a yeast model (Doimo et al 2014b) and studies on mammalian cells are ongoing.

When to suspect CoQ_{10} deficiency?

Primay CoQ_{10} deficiency is rare, nevertheless an early diagnosis is essential to ensure that patients receive the appropriate treatment (Montini et al 2008). CoQ_{10} deficiency should be suspected in patients with SRNS without mutations in Nephrin or Podocin, especially in those also presenting with deafness or other CNS manifestations (Emma et al 2011). Other suggestive patients are those with clinical features of mitochondrial encephalomyopathies (especially when there is reduced activity of complex I+III and II+III), those with unexplained ataxia, those presenting with subacute exercise intolerance and weakness, or with signs of lipid accumulation in muscle (Trevisson et al 2011), and those with chromosomal rearrangements involving chromosome 9q34 (Salviati et al 2012).

Because the diagnostic process in these forms may require months, in the suspicion of CoQ_{10} deficiency we advise to collect the appropriate biological samples for the diagnosis (skin fibroblasts and if possible muscle biopsy) and to start immediately the supplementation (which can be suspended if after 1 or 2 months there is lack of an evident clinical response).

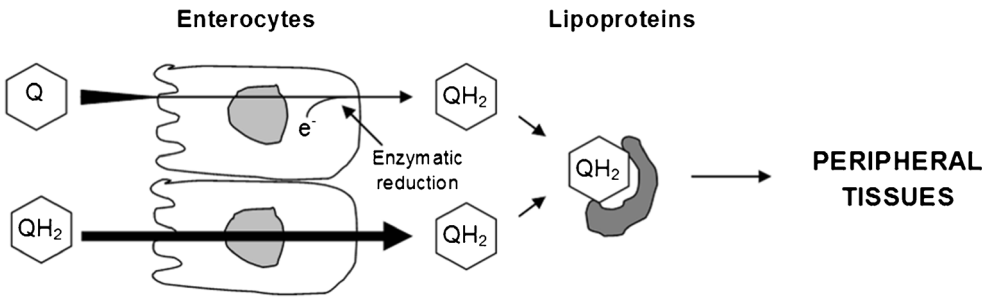

Fig. 4 Absorption and delivery of CoQ to tissues. Ubiquinone (QH) is reduced to ubiquinol (QH_2) upon absorption and then transferred to lipoproteins. Ubiquinol appears to have a better bioavailability than ubiquinone but the exact dose equivalence is unclear

Conclusion

Despite the advances in the past decade there are still many open issues concerning CoQ_{10} deficiency. In particular, therapy is still administered empirically and there is no practical way to monitor its effectiveness (besides the clinical evaluation of patients). Moreover the knowledge on the biosynthetic pathway and its regulation is still limited. A better understanding of these processes could be important to identify other conditions potentially associated with secondary CoQ_{10} deficiency, and to develop novel therapeutic approaches based on stimulation (or reactivation) of the residual CoQ_{10} biosynthesis in patients cells.

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Compliance with ethical guidelines

Conflict of interest None.

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