Coenzyme Q10 (CoQ10) is an essential electron carrier in the mitochondrial respiratory chain and an important antioxidant. Deficiency of CoQ10 is a clinically and molecularly heterogeneous syndrome, which, to date, has been found to be autosomal recessive in inheritance and generally responsive to CoQ10 supplementation. CoQ10 deficiency has been associated with five major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) cerebellar ataxia, (4) isolated myopathy, and (5) nephrotic syndrome. In a few patients, pathogenic mutations have been identified in genes involved in the biosynthesis of CoQ10 (primary CoQ10 deficiencies) or in genes not directly related to the biosynthesis of CoQ10 (secondary CoQ10 deficiencies). Respiratory chain defects, ROS production, and apoptosis contribute to the pathogenesis of primary CoQ10 deficiencies. In vitro and in vivo studies are necessary to further understand the pathogenesis of the disease and to develop more effective therapies.

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**Key Words:** coenzyme Q10; respiratory chain activity; ROS; oxidative stress

Coenzyme Q or ubiquinone is a lipophilic molecule present in all tissues and cells that is located mainly in the inner mitochondrial membrane. It is composed of a redox active benzoquinone ring conjugated to an isoprenoid chain. The length of the chain differs among species; in humans, ubiquinone contains predominantly 10 isoprenyl units and is designated CoQ10. CoQ shuttles electrons from complex I and II to complex III of the mitochondrial respiratory chain; it also functions as a lipid-soluble antioxidant, scavenges reactive oxygen species, and is involved in multiple aspects of cellular metabolism [Turnunen et al., 2004].

Current knowledge of the CoQ biosynthetic pathway in eukaryotes is mostly derived from characterization of CoQ-deficient mutant strains of *Saccharomyces cerevisiae* [Kawamukai, 2009]. The benzoquinone ring is derived from tyrosine, whereas the polyisoprenoid tail is assembled by polypropenylphosphate synthase. Then, polypropenyl diphosphate:4-HB transferase catalyzes the formation of covalent linkage between the benzoquinone head group and the isoprenoid tail, followed by modifications of the aromatic ring (Fig. 1). Ten complementation groups of CoQ yeast mutants have been identified, and mammalian homologues of the yeast Coq genes 

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hypogonadism [Musumeci et al., 2001; Lamperi et al., 2003; Gironi et al., 2004; Artuch et al., 2006; Lagier-Tourenne et al., 2008; Mollet et al., 2008]. Partial CoQ10 deficiency was documented in muscle and in most fibroblasts (9/11) and lymphoblasts (2/3). Although muscle biopsies did not show abnormal mitochondrial proliferation or lipid storage in the first reports [Musumeci et al., 2001; Lamperi et al., 2003], skeletal muscle in one of the patients reported later revealed mitochondrial accumulation and lipid droplets in 10–20% of the fibers [Mollet et al., 2008]. A subgroup of patients with juvenile-onset cerebellar ataxia has primary CoQ10 deficiency due to ADCK3/CABC1 mutations [Lagier-Tourenne et al., 2008; Mollet et al., 2008]. Secondary CoQ10 deficiency has been found to result from a stop codon mutation in the APTX gene encoding aprataxin [Quinzii et al., 2005; Le Ber et al., 2007], which is a protein involved in double-stranded DNA repair [Reynolds et al., 2009] and is known to cause ataxia-oculomotor-apraxia 1 (AOA1) [Date et al., 2001; Moreira et al., 2001]. In these patients, CoQ10 deficiency was not correlated with disease duration, severity, or progression or with biological measures, indicating that CoQ10 deficiency is not the primary or the only cause of neurological decline in AOA1. Nevertheless, three patients improved considerably after CoQ10 supplementation [Quinzii et al., 2005].

**Multisystemic Infantile Form**

In contrast to the ataxic form, most patients with the multisystemic infantile form have had genetically confirmed primary CoQ10 deficiency. The infantile-onset disorder was described initially in 2000 by Rötig et al. in three siblings who presented soon after birth with neurological symptoms, including nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, weakness, and rapidly progressive nephropathy [Rötig et al., 2000]; however, the causative mutation in this family has not been reported. In 2006, we reported the first mutation causing primary CoQ10 deficiency in a proband with infantile-onset multisystemic disease and his younger sister, who shared a homozygous missense mutation in the COQ2 gene encoding para-hydroxybenzoate-polyprenyl transferase [Quinzii et al., 2006]. The elder sibling was a 33-month-old boy who was noted to have nystagmus at 2 months. At 12 months, he was hospitalized because of a severe nephrotic syndrome and neurological examination showed hypotonia and mild psychomotor delay. At 18 months, he developed frequent vomiting, psychomotor regression, tremor, weakness, hypotonia, and status epilepticus. Brain MRI showed cerebral and cerebellar atrophy and stroke-like lesions. He received a successful renal transplant at 3 years of age. The sister developed nephrotic syndrome at 12 months of age without any clinical signs of neurological involvement [Salviati et al., 2005; Diomedi-Camassei et al., 2007]. Both siblings improved with CoQ10 supplementation [Diomedi-Camassei et al., 2007; Montini et al., 2008].

![CoQ10 biosynthesis pathway. CoQ10 is composed of a benzoquinone ring and a decaprenyl side chain. ADCK3 (CABC1) is a kinase that modulate CoQ10 synthesis, possibly through phosphorylation of COQ3 [Tauche et al., 2008]. The function of COQ9 is unknown.](image-url)
Rötig and colleagues also reported a girl with neonatal neurologic
distress, nephrotic syndrome, hepatopathy, pancytopenia, diabetes, seizures, and
lactic acidosis progressing to fatal multiorgan failure at age 12 days [Mollet et al., 2007]. The older brother
also had anemia, liver failure, and renal insufficiency and died at the age of 1
day. Both siblings harbored a homozygous base-pair deletion in exon 7 of the
COQ2 gene.

Mutations in PDSS2, which encodes one of two subunits of proprenyl
diphosphate synthase, the first enzyme of the CoQ10 biosynthetic pathway, have been reported in a male infant
with nephrotic syndrome and Leigh syndrome [Lopez et al., 2006]. The boy presented with neonatal pneumonia and
hypotonia. At 3 months of age, he developed seizures and subsequently became progressively floppy, had difficulty
feeding, severe episodic vomiting, and lactic acidosis and died at age 6 months due to severe refractory focal
status epilepticus. In a consanguineous family, two siblings had CoQ10 deficiency due to a homozygous PDSS1
mutation manifesting as a multisystem disease with early-onset deafness, encephaloneuropathy, obesity, livedo reticu-
laris, and cardiac valvulopathy [Mollet et al., 2007].

Last year, Duncan and colleagues reported mutations in another gene, COQ9, required for the biosynthesis of
CoQ10 in a boy presented at 6 hr of age with poor feeding, hypothermia, and "shaking of both arms" [Rahman
et al., 2001; Duncan et al., 2009]. He had generalized limb hypertonia with reduced truncal tone, lactic acidosis, renal
tubulopathy, and cardiomyopathy. Brain MRI revealed cerebral and cerebellar atrophy. He developed severe
seizures and dystonia and died at 2 years of age.

In all of the infantile multi-systemic syndromes, levels of CoQ10 were decreased in muscle and fibroblasts.

COQ2 gene [Diomedi-Camassei et al., 2007]. The first patient presented with steroid-resistant nephrotic syndrome at
age 18 months as a result of collapsing glomerulopathy, without extra-renal manifestations. The second patient pre-
sented at 5 days of life with oliguria, had severe extracapillary proliferation on renal biopsy, rapidly developed end-
 stage renal disease, and died at the age of 6 months after a course complicated by progressive epileptic encephalopathy.
Combined complex II + III activity and CoQ10 level were decreased in renal cortex as well as in skeletal muscle
[Diomedi-Camassei et al., 2007].

Myopathy
Finally, two groups have described a pure myopathic form, with lipid storage
myopathy and respiratory chain dysfunction [Lalani et al., 2005; Horvath et al., 2006]. In 2007, Gempel and col-
leagues [Gempel et al., 2007] found in the patients reported by Horvath and colleagues mutations in the $ETFDH$

In all of the infantile multi-systemic syndromes, levels of CoQ10 were decreased in muscle and fibroblasts.

diabetic aciduria type II (multiple acyl-CoA dehydrogenase deficiency [MADD]). In that report, all seven patients from five
families presented with exercise intolerance, fatigue, proximal myopathy, and high-serum CK. Muscle histology
showed lipid storage and subtle signs of mitochondrial myopathy. In contrast, other studies reported patients with
MADD and $ETFDH$ mutations who had normal CoQ10 levels in muscle [Liang et al., 2009; Ohkuma et al., 2009].

Other Clinical Presentations
In addition to the main phenotypes described above, CoQ10 deficiency has been reported in two adults
with childhood-onset Leigh syndrome encephalopathy, growth retardation,
infantilism, ataxia, deafness, and lactic acidosis [Van Maldergem et al., 2002]. CoQ10 deficiency has also been
reported in a patient with cardiofacio-

Quinzii et al., 2006; Diomedi-Camassei et al., 2007]. He
devolved seizures and rapidly developed end-stage renal disease, and died at the age
of 6 months after a course complicated by progressive epileptic encephalopathy.

Moreover, CoQ10 deficiency has been reported in patients with a variety of mitochondrial diseases including mito-
ochondrial DNA depletion [Matsuoka et al., 1991; Montero et al., 2005; Miles et al., 2008; Sacconi et al., 2010].

DIAGNOSIS AND TREATMENT
The content of CoQ in organs and membranes depends on functional
requirements. It exhibits great variations not only in different tissues but also
within the same organ and among membranes of individuals. Moreover, tissue levels of CoQ10 depend mainly
on de novo synthesis [Dallner and Sinder, 2000]. In contrast, plasma concentrations of CoQ10 are significantly
influenced by diet and uptake. Because plasma concentrations may not adequately represent cellular
concentrations, bone cells and platelets may be suitable for assessing intracellular CoQ10
concentration for ubiquinone deficiency in treatment-naïve patients [Niklowitz et al., 2004, 2007; Miles et al., 2008].
Deficiency of CoQ10 in skin fibroblasts can be an important confirmation of a primary defect of CoQ10 biosynthesis in
patients with multisystemic disease; however, normal levels of CoQ10 in fibroblasts do not exclude deficiency of
CoQ10 in muscle [Lagier-Tourenne et al., 2008; Montero et al., 2008].

Therefore, direct measurement of CoQ10 levels in muscle is the most reliable
test for diagnosis. Reduced biochemical activities of complexes I + III
(NADH:cytochrome $c$ oxidoreductase) and II + III (succinate:cytochrome $c$
oxidoreductase) in the presence of normal activities of isolated complex I
and III suggest severe CoQ10 deficiency, although activities of these enzymes
may be normal with partial ubiquinone deficiency.

Although early supplementation in patients with COQ2 mutations appears to alleviate the nephropathy and may prevent development of neurologi-
cal signs and symptoms [Montini et al., 2008], patients with PDSS2 and COQ9

Glomerulopathy
Diomedi-Cassadei and colleagues reported two patients with early-onset
glomerulopathy due to mutations in the gene encoding electron-transferring-fla-
voprotein dehydrogenase, which previously had been associated with glutaric
diaciduria type II (multiple acyl-CoA dehydrogenase deficiency [MADD]).
pathogenesis of primary CoQ10 deficiency: in vitro and in vivo studies

In addition to shutting electrons in the mitochondrial respiratory chain, CoQ10 serves several additional cellular functions including transfer of electrons in plasma membranes [Sun et al., 1992] and lysosomes [Gille and Nohl, 2000], modulation of apoptosis [Fontaine et al., 1998; Walter et al., 2002], proton transport of uncoupling proteins [Echtray et al., 2000], and antioxidant activity including inhibition of lipid peroxidation [Villalba et al., 2001] although under certain conditions CoQ may serve as a pro-oxidant [Benninger et al., 2007]. Consequently, deficiency of CoQ10 may disrupt several vital cellular functions. Studies of skeletal muscle biopsies from patients with all forms of CoQ10 deficiency have shown variable defects of respiratory chain enzyme activities (coupled complexes I + III and II + III) [Ogasahara et al., 1989; Musumeci et al., 2001; Lamperti et al., 2003; Lalani et al., 2005; Horvath et al., 2006]. In addition, muscle from patients with myopathic CoQ10-deficiencies has revealed increased markers of apoptosis including increased DNA fragmentation by terminal deoxynucleotidyl transferase mediated dUTP nick end-labeling (TUNEL), increased expression of pro-apoptotic FAS proteins, and activation of caspase 3 [Di Giovanni et al., 2001; Horvath et al., 2006]. Lopez-Martín and colleagues showed that COQ2 mutant fibroblasts require uridine to maintain growth and proposed that deficiency of CoQ10 caused a defect of de novo pyrimidine biosynthesis because of the dependence of dihydro- orotate dehydrogenase on ubiquinol [Lopez-Martín et al., 1997].

Initial studies of cultured fibroblasts from two siblings with infantile-onset CoQ10-deficiency showed mild respiratory chain defects but no evidence of increased superoxide anions, lipid peroxidation, or apoptosis-mediated cell death [Geronemul et al., 2001]. To explore these putative pathogenic mechanisms, we have investigated the consequence of severe CoQ10 deficiency on bioenergetics, oxidative stress, and antioxidant defenses in cultured skin fibroblasts harboring COQ2 and PDSS2 mutations. These studies suggest that defects in the first two committed steps of the CoQ10 biosynthetic pathway produce different biochemical alterations. PDSS2 mutant fibroblasts have 12% CoQ10 content and 28% residual CI + III activity relative to con-
trol cells with markedly reduced ATP synthesis, but do not show increased ROS production, signs of oxidative stress, or increased antioxidant defense markers. In contrast, COQ2 mutant fibroblasts have 30% CoQ10 content and 48% residual CII + III activity with mild defects of ATP synthesis and show significantly increased ROS production as well as oxidation of lipids and proteins [Quinzi et al., 2008b]. To better understand the pathogenesis of COQ10 deficiency, we have now characterized the effects of varying severity of COQ10 deficiency on ROS production and mitochondrial bioenergetics in additional cells harboring genetic defects of COQ10 biosynthesis. We have observed a correlation between levels of CoQ10 and ROS production: 10–15% or >60% residual CoQ10 content are not associated with significant ROS production, whereas 30–50% residual CoQ10 content is associated with minimal increases in ROS production and cell death. These studies confirm that varying degrees of COQ10 variably impair ATP synthesis and induce oxidative stress [Quinzi et al., in press].

Although studies of both muscle biopsies and cultured fibroblasts indicate that COQ10 deficiency impairs oxidative phosphorylation, activates apoptosis, and induces oxidative stress, pathogenic effects may be cell-specific and the relative contributions of each pathway to cell death are unknown. A role of tissue-specificity in COQ10 deficiency is supported by studies in the kd/kd mice with a spontaneous missense mutation (called kidney disease) in the Pdo2 gene [Lyon and Hulse, 1971; Peng et al., 2008]. Homozygotes for the kd allele appear healthy for the first 8 weeks of life but then develop a lethal kidney disease [Lyon and Hulse, 1971; Peng et al., 2004; Madaio et al., 2005]. Extensive phenotypic evaluation of mice older than 120 days failed to detect any overt extra-renal disease manifestations, suggesting that early mortality from kidney failure precluded additional manifestations of COQ10 deficiency that might have otherwise developed over time [Peng et al., 2008]. Saiki and colleagues noted evidence suggesting a primary role of oxidative stress in the pathogenesis of the disease in the kd/kd mice [Saiki et al., 2008].

Autophagy may also play a role in the pathogenesis of COQ10 deficiency. Rodriguez-Hernandez and colleagues studied four cell lines from patients with COQ10 deficiency, two carrying COQ2 mutations, and two with unknown molecular defects. They observed increased levels of lysosomal markers as well as enhanced expression of transcriptional and translational levels of autophagy genes [Rodriguez-Hernandez et al., 2009]. Because inhibition of autophagy resulted in apoptotic cell death, the authors suggested that autophagy is a protective mechanism involved in the degradation of dysfunctional mitochondria. Interestingly, findings of mitophagy and upregulation of autophagy were also noted in liver-conditional Pdo2 knockout mice [Peng et al., 2004, 2008].

CONCLUSIONS

CoQ10 deficiencies are clinically and genetically heterogeneous diseases that are potentially treatable and therefore important to diagnose early. In vitro studies from our and other groups have revealed that COQ10 deficiency leads to diverse biochemical consequences that play different roles in the demise of mutant fibroblasts. Further studies on the pathogenesis of COQ10 deficiency in patients with different molecular defects and in animal models will lead to improved therapies in patients.

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