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Coenzyme Q and Mitochondrial Disease

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Abstract

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 CoQ₁₀ biosynthesis (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.

Keywords

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 oxygen reactive species, and is involved in multiple aspects of cellular metabolism [Turunen 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 polyprenyldiphosphate synthase. Then, polyprenyl 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 (*COQ* in humans) have been identified via sequence homology [Tran and Clarke, 2007; Kawamukai, 2009].

CoQ₁₀ deficiency causes clinically heterogeneous diseases. In most cases, family history suggests an autosomal recessive mode of inheritance, because siblings are often affected, whereas parents are typically unaffected and sometimes consanguineous. In 18 patients,

pathogenic mutations in genes encoding for proteins involved in the biosynthesis of CoQ₁₀ have been identified (primary CoQ₁₀ deficiencies) [Lopez et al., 2006; Quinzii et al., 2006; Diomedi-Camassei et al., 2007; Mollet et al., 2007, 2008; Lagier-Tourenne et al., 2008; Duncan et al., 2009]. Most patients respond to CoQ₁₀ supplementation [Quinzii et al., 2008a; Duncan et al., 2009].

CLINICAL AND MOLECULAR HETEROGENEITY OF CoQ₁₀ DEFICIENCY

Encephalomyopathy

In 1989, Ogasahara and colleagues reported the first patients with CoQ₁₀ deficiency. Two sisters presented with mitochondrial myopathy, elevated serum creatine kinase (CK), recurrent myoglobinuria, lactic acidosis, and central nervous system signs (seizures and mental retardation) that was associated with decreased activities of complexes I + III and II + III and markedly reduced CoQ₁₀ in muscle [Ogasahara et al., 1989]. Since then, several patients with encephalomyopathy manifesting the same clinical triad of mitochondrial myopathy, recurrent myoglobinuria, and encephalopathy have been described [Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001; Aure et al., 2004]. Among this group of patients, molecular defects have been found in only one patient who carries mutations in the *ADCK3/CABC1* gene [Aure et al., 2004; Mollet et al., 2008], the human ortholog of the yeast *Coq8* gene. *ADCK3* encodes a putative mitochondrial kinase thought to be involved in the regulation of the biosynthesis of CoQ, possibly by phosphorylating Coq3 protein (Coq3p) [Iizumi et al., 2002; Tauche et al., 2008].

Childhood-Onset Cerebellar Ataxia and Atrophy

In 2001, Musumeci and colleagues described the most common phenotype associated with CoQ₁₀ deficiency, which is characterized by childhood-onset cerebellar ataxia and atrophy; other variably associated manifestations include: neuropathy, seizures, mental retardation, muscle weakness, and hypogonadism [Musumeci et al., 2001; Lamperti 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; Lamperti 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 parahydroxybenzoate-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; Diomed-Camassei et al., 2007]. Both siblings improved with CoQ₁₀ supplementation [Diomed-Camassei et al., 2007; Montini et al., 2008].

Rötig and colleagues also reported a girl with neonatal neurological 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 polyprenyl 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 8 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 reticularis, 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 who 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. Noteworthy, all patients with *PDSS1*, *PDSS2*, *COQ2*, and *COQ9* mutations had renal disease [Lopez et al., 2006; Quinzii et al., 2006; Diomed-Camassei et al., 2007; Mollet et al., 2007; Duncan et al., 2009] as did *Pdss2* mutant mice that show glomerulonephritis as the sole clinical manifestation [Peng et al., 2008].

Glomerulopathy

Diomed-Cassadei and colleagues reported two patients with early-onset glomerulopathy due to mutations in the *COQ2* gene [Diomed-Camassei et al., 2007]. The first patient presented with steroid-resistant nephrotic syndrome at age 18 months as a result of collapsing glomerulopathy, without extrarenal manifestations. The second patient presented 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 [Diomed-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 colleagues [Gempel et al., 2007] found in the patients reported by Horvath and colleagues mutations in the *ETFDH* gene encoding electron-transferring-flavoprotein dehydrogenase, which previously had been associated with glutaric 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 adult sisters 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 cardiofaciocutaneous syndrome due to a *BRAF* mutation [Aeby et al., 2007]. Leshinsky-Silver and colleagues reported a patient who presented with neonatal liver disease, pancreatic insufficiency, tyrosinemia, hyperammonemia, subsequent sensorineural hearing loss, and Leigh syndrome [Leshinsky-Silver et al. 2003]. Liver biopsy revealed markedly reduced complexes I + III and II + III activities that were restored by addition of CoQ₁₀ to the liver homogenate indicating ubiquinone deficiency.

Moreover, CoQ₁₀ deficiency has been reported in patients with a variety of mitochondrial diseases including mitochondrial 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 Sindelar, 2000]. In contrast, plasma concentrations of CoQ₁₀ are significantly influenced by dietary uptake. Because plasma concentration may not adequately represent cellular concentrations, blood 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 neurological signs and symptoms [Montini et al., 2008], patients with *PDSS2* and *COQ9* mutations described by Lopez et al. and Rahman et al. died despite CoQ₁₀ replacement. CoQ₁₀ treatment was accompanied by mild, subjective, clinical improvement in patients with cerebellar ataxia associated with mutations in *ADCK3/CABC1* [Rahman et al., 2001; Lopez et al., 2006; Lagier-Tourenne et al., 2008;

Mollet et al., 2008; Duncan et al., 2009]. All the patients with pure myopathy showed dramatic improvements after CoQ₁₀ supplementation [Gempel et al., 2007]. Interestingly, in patients with the encephalomyopathic form treated with CoQ₁₀ supplementation, all showed improvements of muscle symptoms, while only some had nervous system improvements. The lack of improvement of cerebellar symptoms may be due to poor transfer of CoQ₁₀ across the blood-brain barrier, irreversible structural alterations in the cerebellum, or both [Bentinger et al., 2003].

In general, disparate responses to CoQ₁₀ supplementation suggest differences in the pathophysiologic mechanisms of these disorders and/or in the pharmacokinetics of CoQ₁₀ supplementation.

CoQ₁₀ is a lipophilic molecule, which accumulates in membranes reaching saturated concentrations. Thus, only a small proportion reaches the mitochondria. In addition, much of the CoQ₁₀ in mitochondria is likely to be trapped in the outer membrane and, consequently, not available to the respiratory chain, which is located in the mitochondrial inner membrane [Geromel et al., 2002].

We have evaluated the in vitro efficacy of CoQ₁₀ supplementation in normalizing the bioenergetic status and oxidative balance in fibroblasts of CoQ₁₀ deficient patients compared with the efficacy of short-tail ubiquinone analogs (idebenone and CoQ₂), which are less lipophilic, as well as vitamin C, a hydrophilic antioxidant [López et al., in press]. We observed that after 24 hr of 5 μ M CoQ₁₀ supplementation (the approximate concentration reached in the plasma of patients supplemented with high-doses of oral CoQ₁₀), cellular CoQ₁₀ levels increased dramatically and all four compounds significantly reduced superoxide anion levels and cell death in mutant fibroblasts with increased oxidative stress. However, after 24 hr of CoQ₁₀ treatment, none of the cell lines showed significant improvement in ATP levels or in ATP/ADP ratios, which are markers of respiratory chain function. In marked contrast to treatment for 24 hr of CoQ₁₀, incubation of ubiquinone-deficient fibroblasts for 1 week with 5 μ M CoQ₁₀ increased ATP levels and ATP/ADP ratios significantly, indicating normalization of the bioenergetic status.

Similarly, yeast *coq* mutants showed inefficient uptake of exogenous CoQ₆ to the mitochondrial inner membrane, which was reflected in a low-succinate cytochrome *c* reductase activity after 2–15 μ M CoQ₆ supplementation for 48 hr. Complete rescue of growth of the yeast *coq* mutants' supplemented with 15 μ M CoQ₆ was possible after 6–8 days [Do et al., 2001; Jonassen et al., 2002; Santos-Ocaña et al., 2002]. These results suggest that the pharmacokinetic constraints of CoQ₁₀ in reaching the mitochondrial respiratory chain are key limiting factors in determining its efficacy in CoQ₁₀ deficient patients. Furthermore, an in vivo study of *PDSS2* mutant mice treated for 4 months with 100 mg/kg body weight (b.w.)/day or 200 mg/kg b.w./day of water-soluble CoQ₁₀ showed that only the highest dose of CoQ₁₀ improved the renal function in these CoQ deficient animals [Saiki et al., 2008]. Thus, the dose of CoQ₁₀ is another important factor influencing the effectiveness of CoQ₁₀ supplementation in ubiquinone deficient patients.

In contrast to CoQ₁₀, short-tail ubiquinone analogs and vitamin C failed to increase ATP levels and ATP/ADP ratio in patients' cells after both 24 hr and 1 week of treatment. These results are in agreement with previous studies showing that hydrophilic ubiquinone analogs (CoQ₂ and idebenone) or mitochondrial-targeted ubiquinone (MitoQ) are less efficient than hydrophobic ubiquinone analogs in enhancing energy production by the mitochondrial respiratory chain [Degli Esposti et al., 1996a,b; King et al., 2009].

Thus, initial clinical experience and in vitro studies suggest that in CoQ₁₀ deficient patients, early treatment based on early diagnosis is critical to maximize the efficacy of ubiquinone

supplementation. In addition, administration of antioxidants with high bioavailability may be helpful; however, short-tail ubiquinone analogs are not suitable substitutes for CoQ₁₀. An important determinant of efficacy is absorption/bioavailability of CoQ₁₀ in the various available formulations. Therefore, dosage and monitoring of plasma levels and clinical response are important [Bhagavan and Chopra, 2006; Miles, 2007].

PATHOGENESIS OF PRIMARY CoQ₁₀ DEFICIENCY: IN VITRO AND IN VIVO STUDIES

In addition to shuttling 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 [Echtay 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 [Bentinger 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 proapoptotic FAS proteins, and activation of caspase 3 [Di Giovanni et al., 2001; Horvath et al., 2006]. Lopez-Martin 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 de-hydrogenase on ubiquinol [Lopez-Martin et al., 2007].

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 [Geromel 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 CII + III activity relative to control 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 [Quinzii 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 maximal increases in ROS production and cell death. These studies confirm that varying degrees of CoQ₁₀ variably impair ATP synthesis and induce oxidative stress [Quinzii 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 *Pdss2* 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 extrarenal 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. Rodríguez-Hernández 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 autophagic genes [Rodríguez-Hernández 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 *Pdss2* 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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Fig. 1.

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.