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An Overview of Current Mouse Models Recapitulating Coenzyme Q_{10} Deficiency Syndrome

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Abstract
Coenzyme Q (CoQ), also known as ubiquinone, is an essential lipophilic molecule present in all cellular membranes and involved in a variety of cellular functions, in particular as an electron carrier in the mitochondrial respiratory chain and as a potent antioxidant. CoQ is synthesized endogenously through a complex metabolic pathway involving over 10 different components. Primary CoQ_{10} deficiency in humans, due to mutations in genes involved in CoQ biosynthesis, is a heterogeneous group of rare disorders presenting severe and complex clinical symptoms. The generation of mouse models deficient in CoQ is important to further clarify the cellular function of CoQ and to unravel the complexity in the pathophysiological consequences of CoQ deficiency. This review summarizes the current knowledge on mouse models of primary CoQ deficiency.

Coenzyme Q (CoQ, ubiquinone) is a lipophilic molecule present in all cells and involved in many different cellular functions. The most pivotal function of CoQ is to shuttle electrons from complexes I and II to complex III in the mitochondrial respiratory chain, thereby leading to maintenance of the mitochondrial membrane potential and the production of cellular ATP by oxidative phosphorylation. Besides, it is also a cofactor of uncoupling proteins, a potent antioxidant agent and a modulator of the mitochondrial permeability transition pore [Turunen et al., 2004]. CoQ is distributed in all membranes throughout the cell [Crane, 2001] with the highest amounts found in mitochondrial membranes, in particular the inner membrane, lysosomes and Golgi vesicles [Turunen et al., 2004].

CoQ is synthesized endogenously through a complex and only partially elucidated metabolic pathway (fig. 1). Most available information derives from yeast studies, where initially 9 genes *(coq1–9)* have been characterized as essential for CoQ biosynthesis [Tran and Clarke, 2007]. Moreover, recently mitochondrial ferredoxin Yah1 and ferredoxin reductase Arh1 have been found to be also required for CoQ biosynthesis [Pierrel et al., 2010]. CoQ is composed of a benzoquinone ring, derived from tyrosine,

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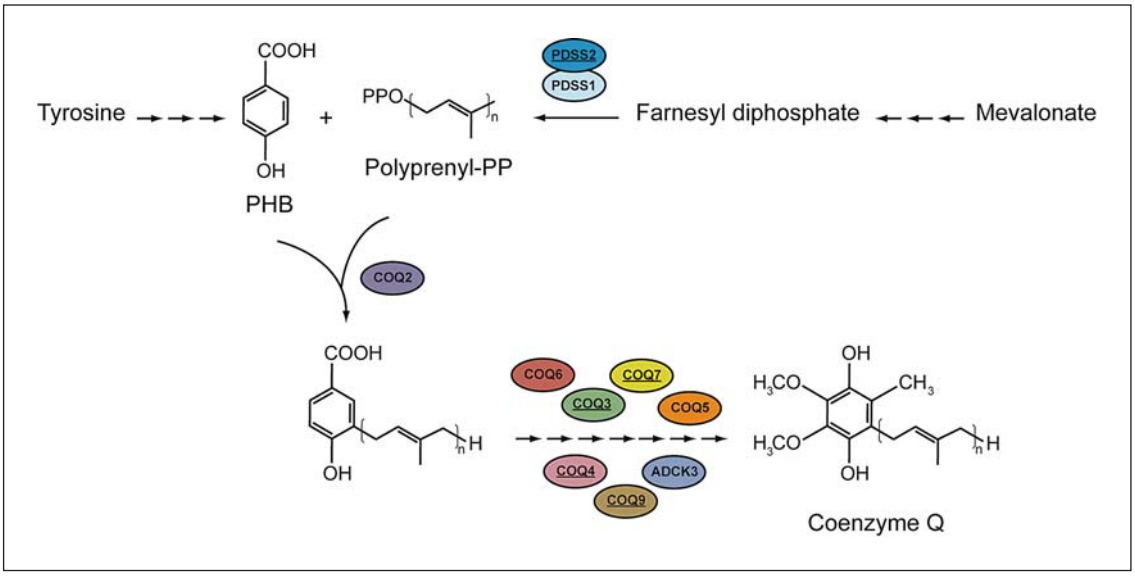

Fig. 1. CoQ biosynthesis in eukaryotic cells. The length of the polyisoprenoid chain (n) varies in different species (n = 9 in mice and n = 10 in humans). PDSS1 and PDSS2 form the *trans*-polyprenyl diphosphate synthase that catalyzes the formation of polyprenyl diphosphate. COQ2 catalyzes the condensation of PHB with polyprenyl-PP. The sequence of modifications of the CoQ aromatic ring is only partially elucidated, and it involves several proteins with different enzymatic or regulatory roles. Underlined are the proteins that have been targeted to produce mouse models. PHB = 4-hydroxybenzoate.

and an isoprenoid side chain (which contains 6–10 isoprene units in different species) generated from acetyl-CoA via the mevalonate pathway [Bentinger et al., 2010]. Briefly, the polyisoprenoid tail is assembled by polyprenyl diphosphate synthase and then covalently bound to the benzoquinone head group producing the 4-hydroxy-3-polyprenyl benzoic acid (4-HB). This is followed by several modifications of the aromatic ring, such as C-hydroxylations, decarboxylation, O-methylations, and C-methylation leading to CoQ [Tran and Clarke, 2007].

Mutations in genes involved in CoQ biosynthesis lead to primary CoQ_{10} deficiency in humans. To date, mutations or deletions in 7 genes involved in the CoQ pathway have been reported: *PDSS1* [Mollet et al., 2007], *PDSS2* [Lopez et al., 2006], *COQ2* [Quinzii et al., 2006; Diomedi-Camassei et al., 2007; Mollet et al., 2007], *ADCK3* [Lagier-Tourenne et al., 2008; Mollet et al., 2008], *COQ4* [Salviati et al., 2012], *COQ6* [Heeringa et al., 2011] and *COQ9* [Duncan et al., 2009], leading to heterogeneous clinical manifestations. The complexity of symptoms associated with CoQ deficiencies has been summarized in 4 main clinical phenotypes [Quinzii and Hirano, 2011]: (I) encephalopathy and encephalomyopathy; (II) severe infantile multisystemic disease; (III) cerebellar ataxia; and (IV) nephrotic syndrome. Moreover, a mitochondrial myopathy is reported in patients with CoQ_{10} deficiency still without a genetic diagnosis [Ogasahara et al., 1989]. The explanation of this marked clinical heterogeneity is still unclear, but it might reflect a tissue-specific regulation of CoQ_{10} biosynthesis, a variable physiological sensitivity of different organs to CoQ_{10} levels or the presence of modifier genes.

Animal Models of CoQ Deficiency

Although studies in yeast and in bacteria have been extremely useful to dissect the biosynthetic pathway of CoQ and to better unravel the multifacet function of CoQ, the generation of multicellular model organisms deficient in CoQ is important to clarify the cellular function of CoQ and to unravel the complexity in the pathophysiological consequences of CoQ deficiency. Invertebrate models have the great advantage to be easily generated and characterized compared to mouse models. Thus, worms and flies lacking CoQ have been produced and they highlighted important functions of CoQ. For instance, *coq-1* knock-down in *Caenorhabditis elegans* causes a specific degeneration of GABAergic neurons, suggesting that this type of neurons are more sensitive

than others to CoQ ablation [Earls et al., 2010]. Moreover, the study of *Drosophila melanogaster* carrying mutations in *qless*, homolog of *PDSS1*, suggested that CoQ promotes the growth of neuroblast lineages, protecting neural cells against mitochondrial stress and apoptosis [Grant et al., 2010].

However, invertebrate systems are not sufficient to reproduce the complexity of mammalian systems. Thus, mouse models deficient in CoQ are extremely valuable and complementary to address the cellular functions of CoQ, the biosynthesis and its regulation and the tissue-specificity that may exist in mammals. Furthermore, mouse models are helpful to study the physiopathology of CoQ deficiencies and to understand the heterogeneity of these syndromes. Finally, the use of mouse models is crucial to test new therapeutic approaches in a first phase of preclinical research.

In this review, we describe the available mouse models for primary CoQ deficiency, i.e. targeting the genes known to be involved in CoQ biosynthesis, and comment on the most important findings that emerged through the study of these models. Table 1 summarizes the mouse models described in this review with the corresponding references.

Table 1. Available mouse models with primary CoQ deficiency

Mouse model	Reference
Spontaneous mutation	
Pdss2$^{kd/kd}$	Lyon and Hulse, 1971; Peng et al., 2004; Madaio et al., 2005
Constitutive knockouts and knock-in	
Pdss2	Peng et al., 2008; Lu et al., 2012
Coq7	Lavavasseur et al., 2001; Nakai et al., 2001
Coq3	Lapointe et al., 2012
Coq4	EUCOMM (http://www.knockoutmouse.org/)
Coq9	EUCOMM (http://www.knockoutmouse.org/)
Coq9 knock-in	Garcia-Corzo et al., 2013
Conditional knockouts	
Pdss2 renal KO	Peng et al., 2008
Pdss2 cerebellar KO	Lu et al., 2012

Constitutive Knockout and Knock-in Mice with Primary CoQ Deficiency

To date, constitutive knockout (KO) mice of only 5 genes implicated in CoQ biosynthesis have been generated (table 1).

Polyisoprenyl diphosphate synthase is the enzyme that catalyzes the formation of the isoprenoid tail of ubiquinone [Tran and Clarke, 2007]. In mice, as well as in humans, this enzyme is composed of 2 subunits encoded by *Pdss1* and *Pdss2,* and it is responsible for the length of the side chain of CoQ [Saiki et al., 2005]. The complete knockout of *Pdss2* is embryonically lethal with no homozygous embryos surviving beyond E9.5 days of gestation, demonstrating the crucial role of CoQ for early development in animals [Peng et al., 2008; Lu et al., 2012].

COQ7 is a demethoxyubiquinone (DMQ) mono-hydroxylase that probably functions in several mono-oxygenase modifications of the benzoquinone ring of CoQ, including the penultimate step [Tran and Clarke, 2007]. Two complete knockouts of *Coq7* (also called *Mclk1*) have been generated and both showed embryonic lethality [Levavasseur et al., 2001; Nakai et al., 2001]. In the first model, *Coq7*$^{-/-}$ embryos failed to survive beyond E10.5, with completely resorbed embryos by E11.5 [Nakai et al., 2001], whereas in the second model, *Coq7*$^{-/-}$ embryos showed a slight developmental delay by E8.5 with condensed and fragmented nuclei suggesting apoptotic cell death, and were completely resorbed by E13.5 [Levavasseur et al., 2001]. In both KO mice, CoQ_9 was not produced in mutant embryos, and its precursor, DMQ_9, was found to accumulate, underlining the crucial role of COQ7 in the biosynthesis of CoQ. Moreover, *Coq7*$^{-/-}$ embryos showed an immature neural tube and disorganization of the neuroepithelium, demonstrating the importance of *Coq7* for neurogenesis. In addition, in the cerebral wall of *Coq7*$^{-/-}$ embryos, mitochondria appeared abnormally enlarged with vesicular cristae [Nakai et al., 2001].

Interestingly, the heterozygous *Coq7*$^{+/-}$ mice are not only completely viable with normal levels of ubiquinone in newborns [Levavasseur et al., 2001], but they display an increased lifespan up to 30% and lower levels of DNA damage in liver [Liu et al., 2005]. Moreover, in very old (25 months) *Coq7*$^{+/-}$ mice, loss of heterozygosity was observed in liver samples, where large groups of cells appeared *Coq7*-negative. At this age, the CoQ_9 content was reduced in liver but not in kidney, however, without accumulation of DMQ_9, suggesting that the CoQ pathway is turned off in adult hepatocytes in the absence of COQ7 [Liu et al., 2005]. A more recent study [Lapointe et al., 2012] has found that although the total amount of CoQ was the same in the mitochondria of *Coq7*$^{+/-}$ mice, the distribution was altered, with a lower than normal level of CoQ_9 in the inner membrane associated with a decrease in the electron transport, and a higher level in the outer membrane. Supplementation with dietary CoQ_{10}

restored the levels of CoQ in the inner membrane as well as the respiratory chain dysfunction.

COQ3 is an O-methyltransferase responsible for the 2 O-methylation steps in ubiquinone biosynthesis, the second and last step [Hsu et al., 1996]. Recently, a constitutive KO mouse for *Coq3* has been generated and, similarly to *Pdss2* and *Coq7* knockouts, resulted in embryonic lethality, although no information as to the age of embryonic lethality was reported [Lapointe et al., 2012]. Furthermore, the heterozygous mouse, in contrast to the *Coq7* heterozygous mouse, exhibited normal life span and normal content of ubiquinone in the mitochondria, suggesting that COQ3 is not limiting in CoQ biosynthesis.

The EUCOMM (http://www.knockoutmouse.org/about/eucomm) program is currently generating KO alleles for other genes involved in CoQ biosynthesis, and to date both *Coq4* and *Coq9* KO lines have been produced.

First evidence shows that *Coq4* KO mice are embryonically lethal. This finding, together with the results of *Pdss2, Coq7* and *Coq 3* complete knockouts, demonstrates the crucial role of CoQ during early development, although it is not clear yet which function of CoQ is required for embryonic development.

In order to better understand the role of CoQ in development, ES cell lines from wild type and *Coq7* KO embryos were generated and characterized. Interestingly, mitochondrial respiratory activity was found to be only mildly affected. In particular, the activity of succinate cytochrome *c* reductase, which involves respiratory complexes II and III, was severely reduced, whereas NADH-cytochrome *c* reductase, which involves respiratory complexes I and III was not strongly affected. Finally, the level of oxygen consumption in mutant ES cells was mildly reduced (65% of wild type). These results, although obtained in cell lines and not in vivo, suggest that DMQ_9 may be able to partially replace CoQ_9 in the respiratory chain. However, the embryonic lethality of $Coq7^{-/-}$ mice suggested that DMQ_9 is unable to completely replace CoQ_9, for one or more of its functions [Levavasseur et al., 2001].

In contrast to the embryonic lethality described in *Pdss2*, *Coq7*, *Coq3*, and *Coq4* constitutive knockouts, *Coq9* KO mice generated by the EUCOMM program are available. An exhaustive phenotyping protocol of the *Coq9* KO mice has started, although very little phenotype has been reported to date. Female *Coq9* KO mice appeared to be hyperactive when monitored for 10 min in an open field arena. The absence of a severe phenotype is surprising and does not correlate with the human phenotype. Indeed, a homozygous nonsense mutation (R244X) in COQ9 has been associated with neonatal-onset lactic acidosis and severe multisystem disease in humans [Duncan et al., 2009]. Albeit *coq9* was identified in yeast as being required for CoQ biosynthesis, the function of the Coq9 protein in the CoQ biosynthesis pathway is unclear, although it has been shown to interact with other Coq polypeptides [Hsieh et al., 2007]. However, recently a *Coq9* knock-in mouse expressing a truncated COQ9 protein has been generated which presents a phenotype resembling human mitochondrial encephalomyopathy associated with CoQ deficiency [Garcia-Corzo et al., 2013]. In particular, *Coq9* mutant mice *($Coq9^{X/X}$)* presented neuronal death in the brain, demyelinization in the pons and the medulla oblongata and astrogliosis. Moreover, $Coq9^{X/X}$ mice showed significant decrease in CoQ_9 and CoQ_{10} in all tissues tested (cerebrum, cerebellum, heart, kidney, liver, and skeletal muscle) combined with an accumulation of DMQ_9, the CoQ precursor substrate of *Coq7* activity. The energy deficit caused by CoQ misregulation leads to increased nucleic acid oxidation and caspase-independent apoptosis in the pons and in the encephalon. Moreover, the heart of mutant mice showed signs of fibrosis, while the kidney did not show any abnormality.

Spontaneous Mutant Mice with Primary CoQ Deficiency

The first reported mutation in *Pdss2* appeared spontaneously in a CBA/CaH colony in the lab of Dr. Mary Lyon, and it was designated 'kidney disease' *(kd)* [Lyon and Hulse, 1971]. Homozygous *kd/kd* mice are apparently healthy for the first 8 weeks of life, but starting at 12 weeks of age, histological analysis of kidneys reveals a mononuclear cell infiltrate and tubular dilatation with proteinaceous casts in cortical areas. This damage extends over time to the entire kidney leading to renal failure. Although an autoimmune mechanism was proposed in earlier studies as the pathophysiological mechanism of the disease [Neilson et al., 1984; Kelly et al., 1986], the work of Hancock et al. [2003] showed that the genetic defect of *kd/kd* mice is intrinsic to the kidney and that the immune response involving either effector T cells or NK cells is a secondary consequence. By positional cloning strategy, the *kd* missense mutation (V117M) was found to fall within exon 2 of the *Pdss2* gene, suggesting for the first time that impairment of CoQ could lead to the renal failure [Peng et al., 2004]. $Pdss2^{kd/kd}$ mice indeed develop

a typical nephrotic syndrome in adult age with albuminuria and lipid abnormalities, such as high levels of serum triglycerides and cholesterol [Madaio et al., 2005].

Conditional KO Mice with Primary CoQ Deficiency

Conditional KO mice are a powerful genetic tool to study the progression of disease and to dissect the different steps of a pathological process, including the primary site of disease development, by allowing the inactivation of genes in a tissue- and/or time-specific manner, overcoming the embryonic lethality issue.

To elucidate the origin of the nephrotic syndrome of *Pdss2*$^{kd/kd}$ mice at the cellular level, tissue-specific conditional *Pdss2* KO mice were obtained by crossing mice carrying the conditional allele (exon 2 flanked by loxP sites) to transgenic mice expressing the Cre recombinase under different promoters. The deletion of *Pdss2* was targeted to renal glomeruli in *Podocin-cre;Pdss2*$^{loxP/loxP}$ mice and to renal tubular epithelium and hepatocytes in *PEPCK-cre;Pdss2*$^{loxP/loxP}$ [Peng et al., 2008]. *Podocin-cre;Pdss2*$^{loxP/loxP}$ mice had a phenotype that resembled that of *Pdss2*$^{kd/kd}$ mice, with serum albuminuria and histological renal defect characterized by dilated tubules and extensive interstitial infiltration. Moreover, *Podocin-cre;Pdss2*$^{loxP/loxP}$ mice had a more severe phenotype than that observed in *Pdss2*$^{kd/kd}$ mice, suggesting that the missense allele in the *Pdss2*$^{kd/kd}$ mice has some residual activity. In contrast, *PEPCK-cre;Pdss2*$^{loxP/loxP}$ did not show any feature of renal abnormalities, suggesting that the primary defect in *Pdss2*$^{kd/kd}$ mice is due to a primary podocyte failure. In particular, *Podocin-cre;Pdss2*$^{loxP/loxP}$ mice showed a diffuse effacement of podocyte foot processes [Peng et al., 2008] as was already observed in *Pdss2*$^{kd/kd}$ mice [Madaio et al., 2005].

The cerebellum is one of the most often affected organs in CoQ deficiency, being involved in 4 out of 5 subtypes. Therefore, in order to dissect the pathological mechanism underlying the cerebellar defects due to CoQ deficiency, as well as to test potential novel dietary CoQ therapies, cerebellar conditional knockouts were generated. Similarly to the work reported by Peng et al. [2008], a conditional allele with loxP site flanking exon 2 was constructed; however, as it is a different conditional allele, the original nomenclature reported is *Pdss2*$^{f/f}$ [Lu et al., 2012]. A first model was generated using the *Pax2-cre* transgenic mice, with the recombinase expressed in the hindbrain region at E9.5 affecting many cell types in the cerebellum at birth, but also strongly expressed in kidney. *Pax2-cre;Pdss2*$^{f/-}$ suffer from neonatal death, with the presence of cerebellar hypoplasia, disorganization of cerebellum and absence of primordial Purkinje neurons at birth. This neonatal growth retardation was caused by a defect in radial cell migration at E12.5 and by ectopic apoptosis starting at E14.5 and increasing until E18.5 [Lu et al., 2012]. Although the severe cerebellum hypoplasia found in the *Pax2-cre;Pdss2*$^{f/-}$ might model the cerebellar atrophy commonly observed in CoQ_{10} infants, the neonatal death precluded studies in adult stages. Therefore, to further analyze *Pdss2* function in adult cerebellum, *Pdss2* was conditionally depleted expressing the Cre recombinase under the *Pcp2* promoter, which is active in cerebellar Purkinje neurons and retinal bipolar neurons from P7 [Lu et al., 2012]. Although *Pdss2* is depleted in Purkinje neurons at 1 month of age, the *Pcp2-cre;Pdss2*$^{f/-}$ mice do not present an impairment of coordination, and there are no morphological abnormalities observed. However, by 6 months of age, the *Pcp2-cre;Pdss2*$^{f/-}$ mice exhibited a significant loss in Purkinje cells and developed a progressive impairment of coordination starting at 9.5 months. Interestingly, dispersed apoptosis was observed in the cerebellum already at 6 months of age, which increased with age, suggesting that Purkinje cell degeneration leads to subsequent diffusive neuron death by apoptosis. This model may serve as a better model to understand the progressive forms of ataxia linked to human CoQ_{10} deficiency in adults.

In agreement with the essential role of CoQ in the respiratory chain, *Pdss2* depletion leads to a strong decrease in CoQ_9 and causes mitochondrial dysfunction, with a significant alteration of the respiratory chain associated with morphological changes of the mitochondria. For example, in cerebellum depleted for *Pdss2*, the mitochondria appeared swollen and with pale matrix [Lu et al., 2012], while in the kidney of *Pdss2*$^{kd/kd}$ mice, the mitochondria were smaller, with compressed cristae and pale matrix [Peng et al., 2004]. Interestingly, both in liver and cerebellum depleted in *Pdss2*, engulfment of mitochondria by ER was observed with the presence of autophagic-like vacuoles, suggesting that mitophagy might be involved to remove abnormal mitochondria [Peng et al., 2004; Lu et al., 2012].

In addition to the renal and cerebellar phenotype, *Pdss2* deletion has also been associated with muscle impairment. In embryonic *Pax2-cre*;*Pdss2*$^{f/-}$ conditional KO mice, lipid accumulation was observed in the forelimb skeletal muscle at P0 [Lu et al., 2012]. Abnormal lipid accumulation in skeletal muscle is a common symptom of CoQ deficiency in humans [Ogasahara et al., 1989;

Horvath et al., 2012], and it may result from a defect in fatty acid metabolism. Interestingly, in liver of *Alb-cre;Pdss2*$^{loxP/loxP}$ conditional KO mice, despite the absence of overt phenotype, fatty acid metabolism was found to be altered together with oxidative phosphorylation, tricarboxylic acid cycle, autophagy and DNA metabolism [Peng et al., 2008]. Some of these pathways were found to be reversed after treatment with probucol, an oral lipophilic antioxidant [Falk et al., 2011].

Conclusions

Several mouse models with deficiency in genes involved in CoQ biosynthesis are available for the study and modeling of primary CoQ deficiencies. These models show a large spectrum of phenotypes, in agreement with the clinical heterogeneity observed in human patients presenting primary CoQ_{10} deficiency. However, as in humans, several organs appear to be more sensitive to CoQ depletion, in particular kidney, cerebellum and muscle. The specific reasons of this tissue sensitivity are not clearly elucidated, but might be linked either to an increased need of CoQ in these tissues and/or to a different tissue-specific expression level of certain genes involved in the biosynthesis of CoQ. Furthermore, the variety of functions associated with CoQ can also play a role in the tissue-specific pathology. These models are important tools for preclinical studies of therapeutic approaches. For instance, probucol and CoQ_{10} have been administered to *Pdss2* mice leading to an improvement in the renal phenotype [Falk et al., 2011]. Surprisingly, an unexpected gender effect was reported in the treatment, with male mice tending to respond better to probucol therapy, whereas females tend to respond better to CoQ_{10}. However, whether this can be translated to humans needs further studies.

To date, only 5 genes involved in CoQ biosynthesis have been targeted and reported, despite the involvement of at least 10 proteins in this process. In order to further dissect the CoQ biosynthetic pathway, and in particular its regulation in mammals, it would be useful to inactivate other genes involved in the pathway, especially those coding for COQ polypeptides whose function has not been elucidated yet. One can speculate that less severe phenotypes might be associated with the inactivation of genes involved in the regulation of the pathway, rather than enzymes involved in specific modifications. To date, *Coq9* depletion is the only gene mutation that is not associated with embryonic lethality, despite the severe clinical presentation in humans. The embryonic lethality associated with most gene deletions so far underlines the crucial role of CoQ during development. To circumvent the embryonic lethality, several conditional KO models have recently been generated and suggest that several functions of CoQ are crucial in vivo in adult tissues, such as its role in energy production through the respiratory chain as well as its antioxidant effect. Finally, although muscle impairment is often associated with CoQ deficit, a muscle-specific conditional knockout has not yet been generated.

In conclusion, mouse models recapitulating CoQ deficiency syndrome are powerful tools to study the pathology of this complex syndrome and to elucidate the biosynthesis of CoQ in mammals. The development of more models in the future, in particular through the large-scale efforts of the international mouse consortium, should provide all the tools necessary to dissect the biosynthesis and regulation of this important and essential molecule.

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