# Coenzyme Q

Subjects: Biochemistry & Molecular Biology

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Coenzyme Q (CoQ), ubiquinone or 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinone is a two-part molecule composed of a benzoquinone ring, which has redox active sites, and a long polyisoprenoid lipid chain that positions the molecule in the mid-plane of a membrane bilayer. It is an essential endogenously synthesized molecule that links different metabolic pathways to mitochondrial energy production thanks to its location in the mitochondrial inner membrane and its redox capacity, which also provide it with the capability to work as an antioxidant.

mitohormesis antioxidant mitochondria anti-aging diet aging-related diseases

## 1. CoQ Biosynthesis

Coenzyme Q (CoQ), ubiquinone or 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinone is a two-part molecule composed of a benzoquinone ring, which has redox active sites, and a long polyisoprenoid lipid chain that positions the molecule in the mid-plane of a membrane bilayer. The length of the chain depends on the species, i.e., 10 isoprene units ($CoQ_{10}$) in humans and *S. pombe*, eight units ($CoQ_8$) in *Escherichia coli*, six units ($CoQ_6$) in *Saccharomyces cerevisiae* and nine units ($CoQ_9$) in rodents. Nevertheless, some species have more than one CoQ form, e.g., human cells and tissues also contain $CoQ_9$ and rodent cells and tissues also contain $CoQ_{10}$ as minor forms.

The synthesis of CoQ in eukaryotes mainly occurs in mitochondria by a set of nuclear-encoded CoQ proteins through a biochemical pathway that has not been fully defined. Moreover, some authors have suggested that CoQ may also be produced outside of mitochondria, mainly in the endoplasmic reticulum-Golgi [1][2]. On the other hand, recent studies suggest that the endoplasmic reticulum mitochondria encounter structure (ERMES) might promote CoQ biosynthesis and the movement of CoQ and its precursors and intermediates between these organelles [3]. Thus, the mitochondrial production of CoQ could contribute to extramitochondrial pools of CoQ. The known steps required for CoQ production were first identified in *S. cerevisiae* and later confirmed in mammals. Specifically, *S. cerevisiae* CoQ (CoQ1–CoQ9) mutants, but also *E. coli* ubi (ubiA-J and ubiX) mutants, have allowed identifying the CoQ genes and biosynthetic intermediaries of the biosynthetic pathway of CoQ [4][5][6][7][8][9]. At least 11 genes (ubiA, B, C, D, E, F, G, H, I, J, and X) in *E. coli* and 13 genes (YAH1, ARH1, and CoQ1–CoQ11) in *S. cerevisiae* are involved in CoQ biosynthesis. Human and mouse orthologues for almost all of these genes have already been identified (with the possible exception of *CoQ11*). In the cases of *CoQ8* and *CoQ10*, humans have two orthologues for each one: *ADCK3* (*CoQ8A*) and *ADCK4* (*CoQ8B*), and *CoQ10A* and *CoQ10B*, respectively. In *Homo sapiens* the polypernyl diphosphate synthase is a heterotetramer formed by the dimer of PDSS1 and PDSS2 proteins [10][11]. The expression of the human homologs (*CoQ1–CoQ10*) for yeast genes restores $CoQ_6$ biosynthesis in the

corresponding *S. cerevisiae CoQ* mutants, indicating the profound functional conservation in human cells [12]. Structurally, CoQ biosynthesis could be divided into four stages: quinone synthesis, isoprenoid tail synthesis, both molecules condensation and ring modification.

## 1.1. Quinone Synthesis

The primary aromatic precursor of the benzoquinone ring is 4-hydroxybenzoic acid (4HB). For the biosynthesis of 4HB, human cells utilize phenylalanine or tyrosine as ring precursors. Many of the steps involved in the generation of 4HB from tyrosine are not completely understood and the responsible enzymes are unidentified [13][14]. Current studies have identified the first and last reactions of this pathway and the enzymes involved in these reactions in yeast. Thus, 4HB synthesis starts with the deamination of tyrosine to 4-hydroxyphenylpyruvate by Aro8 and Aro9 and finishes with the oxidation of 4-hydroxybenzaldehyde to 4HB by Hfd1. Human Hdf1 homolog ALDH3A1 plays a role in CoQ biosynthesis and is able to rescue CoQ deficiency in yeast with the inactivated *HFD1* gene [15][16]. Aro8 and Aro9 human homolog remain unidentified, but α-aminoadipate aminotransferase (AADAT) and the tyrosine aminotransferase (TAT) have been postulated as candidates [17].

Although 4HB is depicted as the main precursor of CoQ, other aromatic ring precursors may be incorporated into CoQ biosynthesis. The 2,4-dihydroxybenzoic acid (2,4-diHB), 3,4-dihydroxybenzoic acid (3,4-diHB) and vanillic acid are analogs of 4HB that may allow the stimulation and/or bypass of CoQ biosynthesis defects in yeast *CoQ6* and *CoQ7* mutants, as well as in *CoQ7* conditional knockout mice, $CoQ9^{R239X}$ mice and human skin fibroblasts from patients with mutations in *CoQ7* and *CoQ9* [18][19][20][21][22][23]. Para-coumarate and resveratrol also can be used as CoQ ring precursors in *E. coli*, *S. cerevisiae*, and human and mouse cells [24]. Moreover, in mouse and human kidney cells, kaempferol is able to increase CoQ levels. This phenolic compound apparently acts as a biosynthetic ring precursor competing with 4HB [25].

## 1.2. Polyisoprenyl Tail Synthesis

The lipophilic polyprenyl tail is synthetized by the addiction of dimethylally pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) to form decaprenyl diphosphate and nonaprenyl diphosphate via PDSS1/PDSS2 in humans and mice. Consequently, the heterotetramer PDSS1/PDSS2 is responsible for the length of the polyprenyl tail. The polyprenyl precursors come from the mevalonate pathway and are generated in the cytosol. The mechanism by which these precursors are transported from the cytosol to mitochondria is unknown, and it has been suggested that some transporters may exist in the inner mitochondrial membrane [17].

## 1.3. Attachment of the Ring/Chain

Furthermore, 4HB and polyprenyl tail are condensed in a reaction catalyzed by human or mice CoQ2 to form 3-decaprenyl-4HB and 3-nonaprenyl-4HB (**Figure 1**a).

## 1.4. Next Steps of CoQ Biosynthesis-Ring Modifications

Then, 3-decaprenyl-4HB or 3-nonaprenyl-4HB undergoes subsequent modifications of the ring through a set or reactions of methylations, decarboxylation and hydroxylations to finally generate the molecule of $CoQ_{10}$ or $CoQ_9$.

The first reaction is the C5-hydroxylation, catalyzed by CoQ6, to produce 3-decaprenyl-4,5-dihydroxybenzoic acid and 3-nonaprenyl-4,5-dihydroxybenzoic acid. In yeast, this step requires two enzymes, ferredoxin Yah1p and ferredoxin reductase Arh1p, which provide electrons for CoQ6 activity. It is unknown whether the mammalian orthologs, ferredoxin reductase (FDXR) and ferredoxin 2 (FDX2), respectively, act in mammalian CoQ biosynthesis. CoQ6 is characterized as a flavin-dependent monooxygenase peripherally associated with inner mitochondrial membrane on the matrix face [26][27].

C5-hydroxylation is followed by O-methylation catalyzed by CoQ3 to form 3-decaprenyl-4-hydroxy-5-methoxybenzoic acid and 3-nonaprenyl-4-hydroxy-5-methoxybenzoic acid. CoQ3 is an S-adenosylmethionine-dependent methyltransferase that is involved in two O-methylation reactions in the CoQ biosynthetic pathway. This polypeptide is also peripherally associated with the mitochondrial inner membrane on the matrix face [28][29].

The proteins involved in the subsequent steps, C1-decarboxylation and C1-hydroxylation, have not been identified in the eukaryotes. However, in prokaryotes the decarboxylation and hydroxylation in prokaryotes are catalyzed by the 3-Octaprenyl-4-hydroxybenzoate decarboxylase UbiD and the 2-octaprenyl-6-methoxyphenol hydroxylase UbiH, respectively [30][31]. In prokaryotic decarboxylation, the flavin prenyltransferase UbiX is important for synthesizing prenylated flavin, which is used as a cofactor for UbiD [32]. Nevertheless, there is no sequence homolog for UbiD or UbiX in humans, suggesting that the C1-hydroxylation could be part of the decarboxylation mechanism.

The ring is then further modified by C2-methylation in a reaction catalyzed by CoQ5. In this reaction, 2-decaprenyl-6-methoxy-1,4-benzenediol and 2-nonaprenyl-6-methoxy-1,4-benzenediol is converted to 2-decaprenyl-3methyl-6-methoxy-1,4-benzenediol and 2-nonaprenyl-3methyl-6-methoxy-1,4-benzenediol ($DMQH_2$) [33]. CoQ5 is an S-adenosyl methionine (SAM)-dependent methyltransferase (SAM-MTase) that is peripherally associated with the mitochondrial inner membrane on the matrix face [34]. $DMQH_2$ is converted to 2-decaprenyl-3methyl-6methoxy-1,4,5-benzenetriol and 2-nonaprenyl-3methyl-6methoxy-1,4,5-benzenetriol ($DMeQH_2$) in a C6-hydroxylation catalyzed by CoQ7, which is a carboxylate bridged diiron hydroxylase peripherally associated with the mitochondrial inner membrane on the matrix side [35].

The final step of the CoQ biosynthetic pathway is an O-methylation also catalyzed by CoQ3.

## 1.5. Other Mitochondrial Proteins Involved in CoQ Biosynthesis

There are additional proteins needed for CoQ biosynthesis since their dysfunctions induce a decline in the levels of CoQ. However, their molecular exact functions are yet unclear. These are the cases of CoQ8A, CoQ8B, CoQ9, $CoQ_{10}$A, $CoQ_{10}$B and CoQ4.

CoQ8A (=ADCK3) and CoQ8B (=ADCK4) have been related with $CoQ_{10}$ biosynthesis and mutations in these proteins are associated with $CoQ_{10}$ deficiency [36][37][38][39]. These two proteins are considered the human orthologues of yeast CoQ8p because $CoQ_6$ biosynthesis is rescued by the expression of human CoQ8A and CoQQB in CoQ8-mutant yeast strains [39][40]. However, the precise biochemical activity and the role of CoQ8 in CoQ biosynthesis remains unknown. Although initially CoQ8 was hypothesized to be a protein kinase that may phosphorylate other CoQ biosynthetic proteins, recent studies have demonstrated that CoQ8A shows ATPase activity that is essential for CoQ biosynthesis. In any case, it seems that the activity of CoQ8A could stabilize Complex Q [41].

CoQ9 is a lipid-binding protein associated with the inner mitochondrial membrane, on the matrix face [42]. This protein binds aromatic isoprenes with high specificity, including CoQ intermediates that likely reside within the bilayer. Therefore, CoQ9 seems to present the intermediates of the CoQ biosynthetic pathway directly to CoQ enzymes [43]. CoQ9 is also necessary for the stability and activity of CoQ7, so *CoQ9* mutant mice and human cells show reduced levels of CoQ7 and accumulation of $DMQH_2$, the substrate of the reaction catalyzed by CoQ7 [23][27][44][45][46].

$CoQ_{10}$A and $CoQ_{10}$B in humans [47] are homologues of the yeast $CoQ_{10}$, a protein that contains a lipid-binding domain that binds CoQ and CoQ intermediates, and that is required for efficient biosynthesis of $CoQ_6$ and electron transport in the mitochondrial respiratory chain. The molecular basis for these effects is unknown, but $CoQ_{10}$ probably directs to CoQ from synthesis site to function sites [48][49][50].

Finally, the function of the CoQ4 is still unknown, although some studies suggest that it is required for the assembly and stability of Complex Q, as it is associated with CoQ3, CoQ5, CoQ6 and CoQ9 [28][51][52]. Also, it is speculated that CoQ4 could bind to CoQ and CoQ intermediates and it could organize the enzymes that perform the ring modifications. In humans, there are two different isoforms of the CoQ4 polypeptide but only one is localized in mitochondria [53].

## 1.6. Complex Q

CoQ biosynthesis depends on a multi-subunit CoQ polypeptide complex formed by several CoQ biosynthetic proteins and by non-proteinaceous components, including some CoQ intermediates and CoQ itself. It is widely accepted that CoQ3–CoQ9 assembly into a high molecular mass complex called Complex Q. These complexes are peripherally associated with the matrix-side of the inner mitochondrial membrane and are essential feature for the de novo biosynthesis of CoQ [17][51][54][55]. In fact, the lack of a single CoQ polypeptide in yeasts, mice and human cells results in the degradation of several CoQ proteins [23][40][42][45][56].

The functional role of Complex Q is to enhance the catalytic efficiency, optimizing the orientation of the substrates and active sites of the enzymes, and to minimize the escape of intermediates, which could be toxic due to their redox or electrophilic properties [17][45][54]. However, many questions about Complex Q remain unknown, including its regulation and the key components involved in its formation and stability.

# 2. Functions of CoQ

The lipophilic characteristic of CoQ together with its redox capacity allows this molecule to participate in multiple cellular pathways and functions.

## 2.1. The Role of CoQ in the Mitochondrial Respiratory Chain

The best-known role of CoQ is its function as an essential electron carrier in the mitochondrial respiratory chain (MRC). CoQ passes electrons between complex I (NADH-ubiquinone oxidoreductase) or Complex II (succinate-ubiquinone oxidoreductase) and Complex III (succinate-cytochrome c oxidoreductase) [57]. Thus, CoQ can be found in both oxidized (CoQ or ubiquinone) and reduced forms ($CoQH_2$ or ubiquinol), and the conversion between these oxidized-reduced states allows it to act as a cofactor of enzymatic reactions transferring electrons to substrates. This oxidation–reduction cycle may occur by a two-step transfer of electrons producing a semiquinone (CoQH·) intermediate.

In mitochondria, CoQ also accepts electrons from sulfide quinone oxidoreductase (SQOR) during sulfide detoxification [58][59][60][61]; proline dehydrogenase 1 (PDH), an enzyme required for proline and arginine metabolism [62]; coline dehydrogenase (CHDH), required for glycine metabolism; mitochondrial glycerol-3-phosphate dehydrogenase (G3PDH), which connects oxidative phosphorylation, fatty acid metabolism and glycolysis [63]; dihydroorotate dehydrogenase (DHOH), an enzyme involved in pyrimidine biosynthesis [64][65][66]; electron transport flavoprotein dehydrogenase (ETFDH), a key enzyme involved in the fatty acid β-oxidation [67]; and hydroxylproline dehydrogenase, involved in the glyoxylate metabolism [68]. All these processes generate $CoQH_2$, which is re-oxidized by complex III. Therefore, CoQ is an excellent redox carrier involved in different cellular processes since it has the ability to sustain continuous oxidation–reduction cycles.

## 2.2. The Antioxidant Capacity

Reactive Oxygen Species (ROS) formed in the cell are able to damage lipids, proteins and DNA. The mitochondrion is the compartment considered to be the major source of ROS production in the cell and, therefore, this organelle is highly susceptible to suffer oxidative damage. To avoid this harmful effect, the mitochondrion possesses antioxidant compounds and systems, being CoQ one of them. CoQ is one of the most powerful endogenously synthesized membrane antioxidants, being present in all membranes. Its antioxidant function efficiently protects lipids from harmful oxidative damage, but also DNA and proteins [69][70].

CoQ is able to prevent lipid peroxidation in most subcellular membranes and its effectiveness to inhibit lipid peroxidation depends on its complex interaction during the peroxidation process. $CoQH_2$ has the ability to both prevent production and eliminate directly lipid peroxyl radicals (LOO), while vitamin E acts by quenching these radicals. Also, $CoQH_2$ regenerates vitamin E from the α-tocopheroxyl radical [71]. CoQ is considered an efficient antioxidant against radicals produced in membranes for its regeneration capacity, its lipid solubility and because of its involvement in the initiation and propagation of lipid peroxidation [72].

CoQ is effective in the prevention of DNA damage as shown by the decreased strand breaks in DNA and other oxidative DNA damage markers in mitochondria [73], which is important for mitochondrial DNA since its oxidative damage is approximately 10-fold higher than nuclear DNA and is not easily reparable. These data are supported by Tomasetti and colleagues [74][75] who showed that $CoQ_{10}$ supplementation inhibits DNA strand break formation and oxidative damage and enhances DNA repair enzyme activities in lymphocytes. Both the antioxidant activity of $CoQ_{10}$ and the role that $CoQ_{10}$ may play in the redox mechanism implicated in the transactivation of DNA repair enzymes could explain the capability of $CoQ_{10}$ to protect DNA from oxidative damage. However, the precise mechanism under these effects remains unclear.

The high efficiency of CoQ as an antioxidant is related to its effective reactivation redox, its ubiquitous distribution, its localization in membranes, its relatively high concentration and the large capacity of the cell to regenerate CoQ at all its locations [76][77].

### 2.3. Other Controversial Functions

It has been suggested that CoQ is one of the compounds influencing the mitochondrial permeability transition pore (PTP). Studies about the regulation of the PTP by ubiquinone analogues show that ubiquinone inhibits the $Ca^{2+}$ dependent PTP opening, which is mediated through a ubiquinone-binding site directly involved in PTP regulation rather than through redox reactions [78]. However, further details about the organization, structure, components and regulation of the PTP are required to understand whether CoQ has a primary function in the PTP. Other mitochondrial components susceptible to being regulated by redox reactions are the uncoupling proteins (UCPs). However, controversial results have been reported regarding to the involvement of CoQ in the regulation of the UCPs [79][80][81][82][83].

## 3. Pathologic Conditions with Decreased Levels of CoQ

The levels of CoQ are quite stable in cells. However, CoQ levels can be severely reduced in a group of mitochondrial diseases called CoQ deficiencies, which are clinically and genetically heterogeneous disorders characterized by a decrease in the levels of CoQ in tissues or cells. If the deficiency is caused by pathogenic mutations in the genes required for $CoQ_{10}$ biosynthesis, it is classified as primary $CoQ_{10}$ deficiencies. Nevertheless, secondary $CoQ_{10}$ deficiencies are caused by mutations in genes unrelated to CoQ biosynthesis or are derived from other physiological processes or pharmacological treatments. The secondary forms are probably more frequent than the primary defects.

CoQ deficiencies cause the inhibition of oxidative phosphorylation and ATP production, since CoQ is an essential component of the mitochondrial respiratory chain. Because CoQ has other roles unrelated to ATP production, CoQ deficiency can impair other vital cellular functions, such as sulfide metabolism [58][59][60], and may induce oxidative damage [46][84][85][86].

### 3.1. Primary $CoQ_{10}$ Deficiencies

Primary ubiquinone deficiency is a subset of mitochondrial diseases caused by autosomal recessive mutations in CoQ genes. Ogasahara et al. [87] described the first patients with primary $CoQ_{10}$ deficiency as two sisters with progressive muscle weakness, fatigability and central nervous system dysfunction, learning disability, and seizures in one and cerebellar syndrome in the other [87]. Since then, approximately 200 patients have been described with pathogenic mutations in PDSS1 [88], PDSS2 [89][90], CoQ2 [88][89][91], CoQ6 [89][92], CoQ7 [22], CoQ4 [93][94][95], CoQ5 [96], CoQ8A [36][37][38], CoQ8B [89][97] and CoQ9 [98] genes. The clinical manifestations are very heterogeneous among different genes and among patients with mutations in individual genes. Multiple organs may be affected and lead to different symptomatology; when the central nervous system (CNS) is affected the clinical manifestations are variable, including encephalopathy, seizures, cerebellar ataxia, epilepsy, intellectual disability, hypotonia, dystonia, spasticity; in kidney, the most common manifestations is steroid-resistant nephrotic syndrome (SRNS); myopathy in muscle and hypertrophic cardiomyopathy in heart. Many symptoms are common to other mitochondrial diseases [99].

## 3.2. Secondary $CoQ_{10}$ Deficiencies

Secondary CoQ deficiencies may affect any of the multiple CoQ biological functions and its connection to other metabolic pathways [100][101]. Low CoQ levels have been observed in a wide spectrum of diseases, such as oxidative phosphorylation (OXPHOS) diseases due to defects in nDNA-encoded proteins, OXPHOS diseases due to defects in mtDNA-encoded proteins and non-OXPHOS diseases (mitochondrial energy metabolism disorders and other non-mitochondrial diseases). Examples of diseases that may display secondary CoQ deficiencies include mitochondrial myopathies, mitochondrial DNA depletion syndrome, multiple acyl-CoA dehydrogenase deficiency (by mutations in *ETFDH*), ataxia-oculomotor apraxia syndrome (by mutations in *APTX*), cardiofaciocutaneous syndrome (by mutations in *BRAF*), methylmalonic aciduria, GLUT1 deficiency syndrome, mucopolysaccharidosys type III, spinocerebellar ataxia-10 (by mutations in *ANO10*) or multisystem atrophy (MSA) [102][103][104][105][106]. The symptoms are highly dependent on the original pathology and the most common symptoms are muscular and central nervous system manifestations. The exact mechanisms by which CoQ deficiency occurs are still unknown but it has been speculated that the low CoQ values in patients with mitochondrial diseases may be explained by a combination of different mechanisms, such as an incomplete or abnormal respiratory chain that may affect the formation of Complex Q linked to the respiratory chain (resulting in alterations in CoQ biosynthesis); an increase in CoQ degradation as a consequence of the oxidative stress derived from OXPHOS dysfunction; an interference with signaling pathways that potentially regulate CoQ biosynthesis; or a general deterioration of mitochondrial function [55][107].

Other diseases such as liver cirrhosis, phenylketonuria, fibromyalgia and cardiomyopathies also present a decrease in plasma CoQ levels [101][108], although this parameter is not reliable for a diagnostic purpose [109]. The use of statins to treat hypercholesterolemia can cause secondary CoQ deficiency because statins inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) in the mevalonate pathway, which is required to produce farnesyl pyrophosphate, an intermediate in CoQ biosynthesis [110]. Also, a decrease in the levels of the components of Complex Q has recently been related to secondary CoQ deficiency in various mouse models of

mitochondrial diseases [111], as well as in muscle and adipose tissue of patients and a mouse model with insulin resistance [112].

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