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# Coenzyme Q – Biosynthesis and functions

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ABSTRACT

In addition to its role as a component of the mitochondrial respiratory chain and our only lipid-soluble antioxidant synthesized endogenously, in recent years coenzyme Q (CoQ) has been found to have an increasing number of other important functions required for normal metabolic processes. A number of genetic mutations that reduce CoQ biosynthesis are associated with serious functional disturbances that can be eliminated by dietary administration of this lipid, making CoQ deficiencies the only mitochondrial diseases which can be successfully treated at present. In connection with certain other diseases associated with excessive oxidative stress, the level of CoQ is elevated as a protective response. Aging, certain experimental conditions and several human diseases reduce this level, resulting in serious metabolic disturbances. Since dietary uptake of this lipid is limited, up-regulation of its biosynthetic pathway is of considerable clinical interest. One approach for this purpose is administration of epoxidated all-*trans* polyisoprenoids, which enhance both CoQ biosynthesis and levels in experimental systems.



## 1. Introduction

Coenzyme Q (CoQ) is present in every membrane of all cells in the body [1]. Under normal physiological conditions all cells biosynthesize functionally sufficient amounts of this lipid. Thus, in contrast to cholesterol, no redistribution via or uptake from the circulation is required. The liver does release a certain amount of newly synthesized CoQ that associates with VLDL and provides circulating lipoproteins with an antioxidant defense, but this pool is not redistributed to other organs. Consequently, measurement of blood levels of CoQ provides only limited information concerning its actual levels in organs and cells. Under various conditions attenuated synthesis results in reductions in these levels and disturbance of normal functions. Since dietary uptake of CoQ is limited to only a few percent, numerous efforts are continuously directed towards the preparations of forms that are taken up more efficiently or substitutes with functional properties similar to those of CoQ and which are taken up into the circulation and cells more extensively.

## 2. Functions of CoQ

Following its isolation and characterization in 1955, CoQ was originally shown to be a necessary component of the mitochondrial respiratory chain two years later. It functions as an electron carrier from complex I and II to complex III and, according to Mitchell's protonmotive Q cycle, production of ubisemiquinone accounts for the energy conservation occurring at coupling site 2 of the respiratory chain [2].

Today, several other important functions are also associated with this lipid.

1. The plasma membrane of most cells contains a CoQ-dependent NADH-oxidase which regulates the cytosolic ratio of $NAD^+$/NADH ratio and ascorbate reduction and is involved in regulation of cell growth and differentiation [3].
2. CoQ is our only lipid-soluble antioxidant synthesized endogenously and efficiently prevents oxidation of proteins, lipids and DNA. Effective enzymatic systems strive continuously to maintain this compound in its active reduced form [4].
3. Opening of the mitochondrial membrane transition pore allows the translocation of molecules as large as 1500 Da in size, which leads to a collapse of mitochondrial functions. CoQ10 is one of the compounds that prevent such pore opening, thereby it is counteracting apoptotic events such as ATP depletion, release of cytochrome c into the cytosol, caspase-9 activation, depolarization of the mitochondrial membrane potential and DNA fragmentation [5].
4. Uncoupling proteins present in the inner mitochondrial membrane can translocate protons from the outside to the inside of this membrane as a result of which the proton gradient formed by the respiratory chain is uncoupled from oxidative phosphorylation and heat is produced instead. These protons are delivered from fatty acids to the uncoupling proteins with

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the assistance of oxidized CoQ, which is thus an obligatory cofactor in this process [6].

5. CoQ exerts multiple anti-inflammatory effects by influencing the expression of NFκB1-dependent genes [7]. Apparently, uptake of CoQ into lymphocytes and monocytes initiates the release of mediators and signal substances into the blood that subsequently modify such expression in a variety of tissues.
6. By protecting LDL from oxidation, this lipid also has anti-atherosclerotic properties. Moreover, it reduces the levels of lipid peroxides associated with lipoproteins in atherosclerotic lesions, as well as the size of such lesions in the aorta. Furthermore, CoQ decreases the levels of β2-integrin CD11b in monocytes, which counteracts monocyte–endothelial cell interactions [8,9].
7. CoQ helps counteract endothelial dysfunction by stimulating endothelial release of nitric oxide [10].
8. CoQ mediates both oxidation of sulfide in yeast and the introduction of disulfide bonds into bacterial proteins.

Consequently, following extensive investigation of the role played by CoQ in mitochondrial respiration and oxidative phosphorylation, for the last two decades the focus has been on other possible functions of this lipid. It is expected that the list presented above will extended in coming years. It should be pointed out that some of these new functions are experimental observations and it remains to be established whether they are also relevant for humans.

The major focus has been on the antioxidant role of CoQ, which is now well established [11]. This compound inhibits lipid peroxidation by preventing the production of lipid peroxyl radicals ($LOO^{\cdot}$) and, moreover, $CoQH_2$ reduces the initial perferryl radical, with concomitant formation of ubisemiquinone and $H_2O_2$. This quenching of the initiating perferryl radicals, which prevent propagation of lipid peroxidation, protects not only lipids, but also proteins from oxidation. In addition, the reduced form of CoQ effectively regenerates vitamin E from the α-tocopheroxyl radical and thereby interferes with the propagation step. Furthermore, during oxidative stress interaction of $H_2O_2$ with metal ions bound to DNA generates hydroxyl radicals and CoQ efficiently prevents the oxidation of bases, which is particularly important in the case of mitochondrial DNA, where such damage is not easily repaired.

The explanation for the exceptionally high efficiency of CoQ as an antioxidant includes its intramembraneous localization, effective reduction/reactivation by a number of cellular systems and general and abundant distribution. Its localization is of central significance, since hydroxyl and superoxide radicals generated in the membrane would otherwise rapidly react with neighboring lipid and protein molecules which necessitates the availability of effective protective agents close to the site of radical production. In contrast to other antioxidants, this compound inhibits both the initiation and propagation of lipid and protein oxidation.

## 3. The mevalonate pathway

Starting from acetyl-CoA, the series of reactions that comprise the mevalonate pathway produces farnesyl-PP, the precursor for cholesterol, CoQ, dolichol and isoprenylated proteins [12] (Fig. 1). In addition, the intermediary isopentenyl-PP is utilized for the synthesis of dolichol and the isoprenoid side-chain of CoQ. Since the initial sequence of reactions leading to all end-products of the mevalonate pathway is identical, it might be expected that synthesis of these various lipids is co-regulated. However, these mevalonate pathway lipids are synthesized at greatly varying rates and in different amounts, indicating that in addition to regulation of the initial reactions, more terminal regulation must also occur. This situation is illustrated by the fact that the half-lives of cholesterol, dolichol and CoQ in the rodent brain are 4080, 1010 and 90 h, respectively [13]. The terminal points of regulation probably involve the branch-point enzymes that utilize FPP, i.e., squalene synthase, *trans*-prenyltransferase, *cis*-prenyltransferase and farnesyl- or geranylgeraniol-protein transferases for cholesterol, CoQ, dolichol and isoprenylated proteins, which are considered to be rate-limiting for the terminal portion of the biosynthetic sequences [14].

The long isoprenoid side-chain of CoQ (which contains 6–10 isoprene units in different species) is synthesized by *trans*-prenyltransferase which condenses FPP with several molecules of IPP, all in the *trans* configuration [15]. The next step involves condensation of this polyisoprenoid side-chain with 4-hydroxybenzoate, catalyzed by polyprenyl-4-hydroxybenzoate transferase. Hydroxybenzoate, which is synthesized from tyrosine or, at least theoretically, from phenylalanine, generally present in excess, so that the rate of this reaction is determined by the availability of the polyisoprenoid chain. In addition to their presence in mitochondria, these initial two reactions also occur in the endoplasmic reticulum and peroxisomes, indicating multiple sites of synthesis in animal cells.

Following condensation, the benzoquinone ring is modified by C-hydroxylations, decarboxylation, O-methylations and C-methylation, a sequence of reactions that has been examined primarily in bacteria and yeast. The functions of several corresponding mammalian genes have been established through complementary recognition in yeast. However, the complete details of CoQ synthesis in animal tissues remain to be elucidated, which will require isolation of the enzymes involved, a feat that has proven to be formidable so far.

Although HMG-CoA reductase is considered to be the central regulatory enzyme of the mevalonate pathway, this enzyme appears to be involved primarily in the regulation of cholesterol synthesis. The principle of the classical flow diversion hypothesis indicates that variation in the size of the FPP pool will mainly influence cholesterol synthesis, since the $K_m$ of squalene synthase for this substrate is high and, thus, if the concentration of FPP decreases, this enzyme is no longer saturated and the rate of cholesterol synthesis is reduced [16]. In contrast, all of the other branch-point enzymes, i.e., *trans*- and *cis*-prenyltransferases, farnesyl- and geranylgeraniol-protein transferases, exhibit low $K_m$'s and remain saturated even when the FPP pool is smaller.

These enzymological differences explain the efficacy of one of our most common classes of drugs, the statins. By inhibiting the HMG-CoA reductase, statins efficiently reduce the size of the FPP pool and thereby lower the rate of cholesterol synthesis. However, in spite of the differences in affinity, all of the other branch-point enzymes can also be affected, probably because these differences are relatively small. Thus, treatment of rodents with statins lowers the levels of CoQ in several organs and also inhibits protein isoprenylation in certain experimental systems [17,18]. Increases in the size of the FPP pool caused by squalestatin-1, an inhibitor of the squalene synthase, stimulate CoQ biosynthesis both in cell cultures and in rats [19,20]. It has been suggested, but not yet proven, that alteration in the synthesis of lipids other than cholesterol are responsible for the relatively common side-effects of statin treatment.

## 4. Up-regulation of CoQ synthesis

In the case of most metabolic pathways a large number of endogenous metabolites play regulatory rolls. Likewise, production of cholesterol, the main product of the mevalonate pathway, is regulated by several different substances, including oxysterols, squalene oxide, farnesol and its derivatives, geranylgeraniol and prenyl phosphates. It thus seems likely that endogenous compounds also regulate the biosynthesis of CoQ.

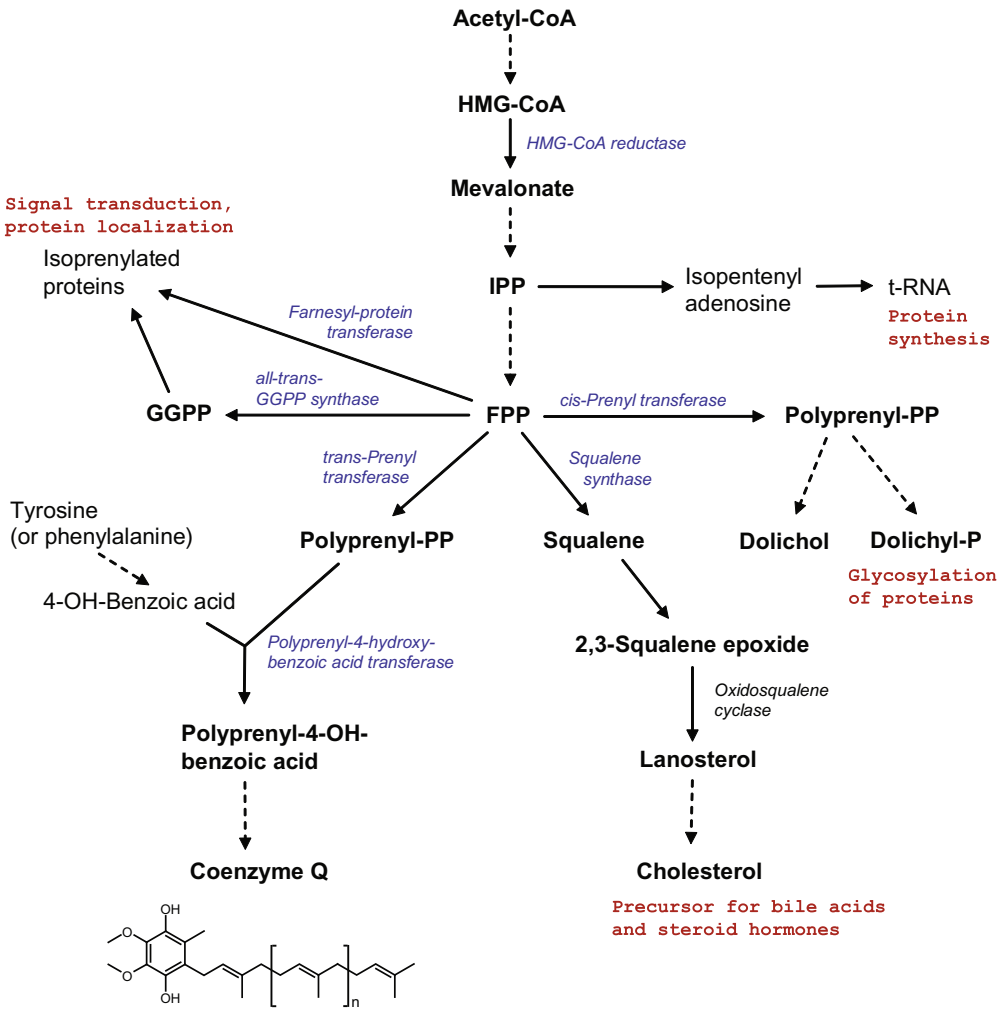


**Fig. 1.** The mevalonate pathway and the terminal steps in the synthesis of CoQ, cholesterol, dolichol and isoprenylated proteins. Red indicates primary functions and blue indicates the rate-limiting enzymes. In the case of CoQ it has not yet been established whether the first or second enzyme in the terminal sequence is rate-limiting.

In HepG2 cells epoxidated derivatives of certain all-*trans* polyisoprenoids, solanesol, tocotrienols, vitamin $K_2$ and CoQ itself all up-regulate CoQ synthesis to various extents and several of these compounds also inhibit cholesterol synthesis by these same cells [21]. None of the epoxidated poly-*cis* polyisoprenoids, which occur naturally without an epoxy group in large numbers, exhibit any effect on products of the mevalonate pathway in this same system.

Tocotrienols, which belong to the vitamin E family, but in contrast to tocopherols contain a side-chain with three isoprene units, exert the most profound effects on these biosynthetic pathways. Analogous to the tocopherols, the α-, β-, γ- and δ-tocotrienols differ with respect to the number and distribution of methyl substituents on the chromanol ring. Their effects on the mevalonate pathway demonstrate a high degree of structural specificity (Fig. 2). For example, the 1-epoxide forms of both α- and γ-tocotrienols have no influence on cholesterol synthesis, whereas the 2-epoxide forms are strongly inhibitory. In the case of CoQ biosynthesis, both epoxy derivatives are effective stimulators. Although dolichol synthesis is also up-regulated, the significance of this finding is unclear, since even though abundant, the non-phosphorylated form of this lipid has no clear-cut function in animals. The enhancement of CoQ biosynthesis reflects up-regulation of the biosynthetic machinery, while the decrease of cholesterol synthesis specifically involves inhibition of oxidosqualene cyclase.

Accordingly, the small amounts of mono- and diepoxide polyisoprenoids present both in animals and other organisms may be one of the biological regulators of the mevalonate pathway. As drugs for human use, these types of compounds might effectively cure many types of CoQ deficiency. The uptake of CoQ from the diet into the blood and from the blood into organs is particularly limited in cases of low-degree deficiency. If its biosynthesis is up-regulated in this manner, not only would the total amount be elevated, but this lipid would have an appropriate localization both at the organelle and intramembranous levels.

## 5. Deficiencies in CoQ synthesis

Some cases of CoQ deficiency in humans result from inactivating mutations in the genes encoding the relevant biosynthetic proteins. Depending on the localization and extent of the defect, the clinical symptoms vary greatly. The brain, cerebellum, muscles and/or kidney may be involved, usually resulting in complex disease patterns [22].

A number of the mutations are characterized, referred to as primary types, directly affect the proteins involved in the biosynthesis of the CoQ [23] (Table 1). Mutations in COOQ1-PDSS1 and -PDSS2 (two subunits of decaprenyl diphosphate synthase), COOQ2 (decaprenyl-4-hydroxybenzoate transferase), COOQ9 (not identified function) and CABC1 or ADCK3 (a putative protein kinase) belong to this group. There are also secondary forms of deficiency caused by mutations in genes not involved in CoQ biosynthesis. Mutations in the APTX (encoding aprataxin) and ETFA (multiple

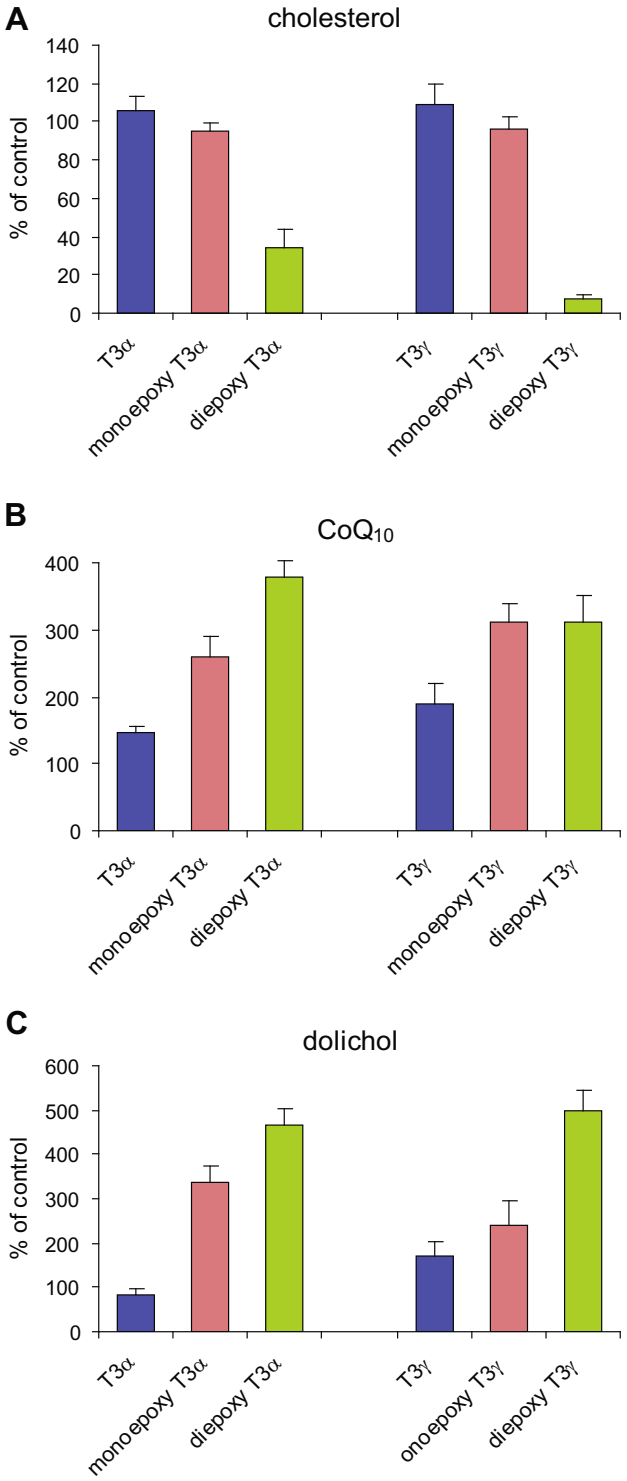


**Fig. 2.** Effects of tocotrienol epoxides on the biosynthesis of cholesterol (A), CoQ (B) and dolichol (C). HepG2 cells in culture were treated with epoxidated forms of tocotrienol (T3)-α and -γ and the rate of synthesis were followed by incorporation of [$^3$H] mevalonate. Blue: tocotrienols; red: tocotrienol monoepoxides; green: tocotrienol diepoxides. Data from [21].

acyl-CoA dehydrogenase deficiency caused by defects in electron transfer flavoprotein or ETF-ubiquinone oxidoreductase) also result in CoQ deficiency. BRAF gene can influence the MAPK pathway in such a way as to lead to the cardiofaciocutaneous syndrome, which is associated with a reduction in the muscle content of CoQ. It is to be expected that the list of gene mutations that directly or indirectly cause CoQ deficiency will become considerably longer in the near future.

**Table 1**
CoQ deficiencies identified in humans.

| Gene mutated | Function of the gene product | Level of CoQ10 (% of control) | |
|---|---|---|---|
| | | Fibroblasts | Muscle |
| *Primary deficiency* | | | |
| COQ1, PDSS1 | Synthesis of decaprenyl-PP | 3 | |
| PDSS2 | | 12 | |
| COQ2 | Condensation of the ring with the side-chain | 24 | 3–38 |
| COQ9 | Unknown | 40 | 15 |
| CABC1 (or ADCK3) | Mitochondrial kinase | 51–63 | 8–29 |
| *Secondary deficiency* | | | |
| APTX | Aprataxin (DNA repair) | 51–68 | 29–66 |
| ETFA, ETFB, ETFDH | Acyl-CoA dehydrogenase | | 10–26 |
| BRAF | Mitogen-activated protein kinase | | 9 |

CoQ deficiency is unique in being the only mitochondrial disease which at present can be successfully treated, in this case by oral supplementation with this lipid. After 6 months of such therapy, children who could not run, throw a ball or climb stairs demonstrate greatly improved cognitive and physical functions [24]. If, however, damage to the brain and kidneys is present at the time of diagnosis, such damage cannot be reversed completely. If the diagnosis is made before symptoms appear, and the treatment is started at this time, the child develops normally without any brain or kidney damages. Consequently, early diagnosis is an absolute necessity, but is presently problematic in that it requires muscle biopsy and subsequent analysis of the mitochondria in this tissue.

## 6. Regulation of tissue levels of CoQ

The actual level of CoQ is determined by a coordinated balance between the synthetic and catabolic enzymes, which are both expressed in all tissues. This lipid is rapidly broken down, as reflected in its short half-life, $T_{1/2}$, of 49–125 h in various tissues and the initial steps in this degradation involve ω-oxidation and subsequent β-oxidation of the side-chain [25]. The primary breakdown product detected in tissues, the urine and feces contains an intact, fully substituted ring, a short side-chain of 5–7 carbon atoms and a carboxylated ω-terminus [26]. CoQ is synthesized in all cells of animal organisms and this is also the case for the breakdown. Derivatization to a water-soluble compound through the relatively uncommon mechanism of phosphorylation, also occurs in individual organs [27]. These metabolites are transported via the circulation to the kidney where they are excreted.

Under a number of physiological, experimental and pathological conditions tissue levels of CoQ are either elevated or depressed [28] (Table 2). In searching for drugs that might cause changes by altering the rates of synthesis and/or degradation, only PPARα agonists have been examined to date and shown to enhance synthesis without altering the rate of breakdown. These compounds are affecting CoQ synthesis in rodents but not in human, probably because of the low level of these receptors.

The tissue levels of CoQ, in addition to synthesis and breakdown, can be influenced by several other factors as well. Since mitochondria are both numerous in most cells and rich in CoQ, modification of the number, size or structural arrangement of this organelle can profoundly modify the tissue content of this lipid without interfering with its metabolism. Two examples are cold adaptation and exercise, in connection with which the number of mitochondria in liver and muscle is increased [29] and this type of alteration appears to occur under other conditions as well.

**Table 2**
Conditions under which total tissue levels of CoQ are altered.

| | Increased | Decreased |
|---|---|---|
| Physiological conditions | Cold adaptation<br>Exercise | Aging |
| Experimental conditions | PPARα agonists<br>LXRα agonists in the liver<br>Thyroxin<br>Vitamin A deficiency<br>Vitamin E<br>Fluoride<br>Squalestatin-1<br>Epoxides of polyisoprenoids | Vitamin A<br>LXRα agonists in<br>the spleen, thymus and lung<br>Selenium deficiency<br>RXRα deficiency<br>Statin treatment |
| Diseases | Preneoplastic nodules<br>Alzheimer's disease<br>Prion disease<br>Diabetes | Liver cancer<br>Cardiomyopathy<br>Nieman-Pick type C disease<br>Parkinson's disease<br>Various complex myopathies |

Since CoQ is present in all cellular membranes and may participate in a specific function(s) at a specific site, the total cellular content of this lipid will not necessarily reveal an excess or deficiency at a specific location. For instance, selenium deficiency is associated with a reduction in the total hepatic content of CoQ, but enhanced levels it in the plasma membrane of hepatocytes [30].

Moreover, rapid changes can probably occur as a result of the distribution of the biosynthetic machinery. Biosynthesis of CoQ is considered to be localized to the inner mitochondrial membrane, but individual enzymes are also present in the endoplasmic reticulum, Golgi system and peroxisomes [31,32]. This broad distribution of the biosynthetic enzymes in animal cells, in contrast to yeast, makes it possible to supply various organelles with newly synthesized CoQ without the involvement of mitochondria. Such creation of local pools of CoQ for specific functions may not be reflected in the total tissue or cellular level. Interestingly, when various functions, most often mitochondrial respiration and oxidative phosphorylation, are measured in experimental and diseased states, there is often no correlation between the reduction in total CoQ level and impairment of a specific, CoQ-dependent function, such as respiration [33]. Apparently, compartmentalization of this lipid at the intracellular and organelle level may vary considerably and, consequently, the degree of saturation of one enzymic system with CoQ may differ greatly from that of another in the same cell.

It is to be expected that the expression of proteins involved in CoQ biosynthesis is regulated by transcriptional factors, analogous to nuclear hormone receptors. In fact, RXRα deficiency in the liver is associated with pronounced reduction in both the level and the rate of synthesis of this lipid, indicating the possible involvement of this receptor in such regulation [34]. RXR functions as a heterodimer, but the other receptor involved here has not yet been identified. PPARα is not required for the basal synthesis of CoQ, but does mediate the effects of peroxisome proliferators on this synthesis [35]. When mice are treated for 6 weeks with di(ethylhexyl)phthalate, an agonist of PPARα, hepatic CoQ content is elevated fivefold and increases are also observed in other organs, although not in the brain. These increases do not occur in PPARα-null mice. Although LXRα is not required either, this receptor can influence the synthetic rate, exerting a positive regulation in the liver and a negative influence in the spleen, thymus and lung (Bentinger and Steffensen, unpublished).

In connection with certain diseases, such as cancer and diabetes, tissue levels of CoQ are elevated [36]. These conditions are associated with oxidative stress and damage caused by free radicals and other reactive oxygen and nitrogen species. It is to be expected that the organism will take protective measures, including increasing the levels of antioxidative compounds and enzymes. Thus elevation of CoQ levels in connection with such disease states can be viewed as an attempt to limit injuries caused by free radical attack.

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## References

[1] M. Turunen, J. Olsson, G. Dallner, Metabolism and function of coenzyme Q, Biochim. Biophys. Acta 1660 (2004) 171–199.
[2] P. Mitchell, Protonmotive redox mechanism of the cytochrome b–c1 complex in the respiratory chain: protonmotive ubiquinone cycle, FEBS Lett. 56 (1975) 1–6.
[3] C. Gomez-Diaz, J.C. Rodriguez-Aguilera, M.P. Barroso, J.M. Villalba, F. Navarro, F.L. Crane, P. Navas, Antioxidant ascorbate is stabilized by NADH-coenzyme Q10 reductase in the plasma membrane, J. Bioenerg. Biomembr. 29 (1997) 251–257.
[4] L. Ernster, Lipid peroxidation in biological membranes: mechanism and implications, in: Active Oxygens, Lipid Peroxides, and Antioxidants, CRC Press, Boca Raton, 1993.
[5] L. Papucci, N. Schiavone, E. Witort, M. Donnini, A. Lapucci, A. Tempestini, L. Formigli, S. Zecchi-Orlandini, G. Orlandini, G. Carella, R. Brancato, S. Capaccioli, Coenzyme q10 prevents apoptosis by inhibiting mitochondrial depolarization independently of its free radical scavenging property, J. Biol. Chem. 278 (2003) 28220–28228.
[6] K.S. Echtay, E. Winkler, K. Frischmuth, M. Klingenberg, Uncoupling proteins 2 and 3 are highly active H(+) transporters and highly nucleotide sensitive when activated by coenzyme Q (ubiquinone), Proc. Natl. Acad. Sci. USA 98 (2001) 1416–1421.
[7] F. Doring, C. Schmelzer, I. Lindner, C. Vock, K. Fujii, Functional connections and pathways of coenzyme Q10-inducible genes: an in-silico study, IUBMB Life 59 (2007) 628–633.
[8] S.R. Thomas, J. Neuzil, R. Stocker, Cosupplementation with coenzyme Q prevents the prooxidant effect of alpha-tocopherol and increases the resistance of LDL to transition metal-dependent oxidation initiation, Arterioscler. Thromb. Vasc. Biol. 16 (1996) 687–696.
[9] M. Turunen, L. Wehlin, M. Sjoberg, J. Lundahl, G. Dallner, K. Brismar, P.J. Sindelar, beta2-Integrin and lipid modifications indicate a non-antioxidant mechanism for the anti-atherogenic effect of dietary coenzyme Q10, Biochem. Biophys. Res. Commun. 296 (2002) 255–260.
[10] G.T. Chew, S.J. Hamilton, G.F. Watts, Therapeutic regulation of endothelial dysfunction in type 2 diabetes mellitus, Diab. Vasc. Res. 4 (2007) 89–102.
[11] M. Bentinger, K. Brismar, G. Dallner, The antioxidant role of coenzyme Q, Mitochondrion 7 (Suppl.) (2007) S41–S50.
[12] J.L. Goldstein, M.S. Brown, Regulation of the mevalonate pathway, Nature 343 (1990) 425–430.
[13] M. Andersson, P.G. Elmberger, C. Edlund, K. Kristensson, G. Dallner, Rates of cholesterol, ubiquinone, dolichol and dolichyl-P biosynthesis in rat brain slices, FEBS Lett. 269 (1990) 15–18.
[14] J. Grunler, J. Ericsson, G. Dallner, Branch-point reactions in the biosynthesis of cholesterol, dolichol, ubiquinone and prenylated proteins, Biochim. Biophys. Acta 1212 (1994) 259–277.
[15] U.C. Tran, C.F. Clarke, Endogenous synthesis of coenzyme Q in eukaryotes, Mitochondrion 7 (Suppl.) (2007) S62–S71.
[16] M.S. Brown, J.L. Goldstein, Multivalent feedback regulation of HMG CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth, J. Lipid Res. 21 (1980) 505–517.
[17] P. Low, M. Andersson, C. Edlund, G. Dallner, Effects of mevinolin treatment on tissue dolichol and ubiquinone levels in the rat, Biochim. Biophys. Acta 1165 (1992) 102–109.
[18] C. Morck, L. Olsen, C. Kurth, A. Persson, N.J. Storm, E. Svensson, J.O. Jansson, M. Hellqvist, A. Enejder, N.J. Faergeman, M. Pilon, Statins inhibit protein lipidation and induce the unfolded protein response in the non-sterol producing nematode *Caenorhabditis elegans*, Proc. Natl. Acad. Sci. USA 106 (2009) 18285–18290.
[19] A. Thelin, E. Peterson, J.L. Hutson, A.D. McCarthy, J. Ericsson, G. Dallner, Effect of squalestatin 1 on the biosynthesis of the mevalonate pathway lipids, Biochim. Biophys. Acta 1215 (1994) 245–249.
[20] R.K. Keller, Squalene synthase inhibition alters metabolism of nonsterols in rat liver, Biochim. Biophys. Acta 1303 (1996) 169–179.
[21] M. Bentinger, M. Tekle, K. Brismar, T. Chojnacki, E. Swiezewska, G. Dallner, Polyisoprenoid epoxides stimulate the biosynthesis of coenzyme Q and inhibit cholesterol synthesis, J. Biol. Chem. 283 (2008) 14645–14653.
[22] A. Rotig, J. Mollet, M. Rio, A. Munnich, Infantile and pediatric quinone deficiency diseases, Mitochondrion 7 (Suppl.) (2007) S112–S121.
[23] C.M. Quinzii, L.C. Lopez, A. Naini, S. DiMauro, M. Hirano, Human CoQ10 deficiencies, Biofactors 32 (2008) 113–118.
[24] A. Rotig, E.L. Appelkvist, V. Geromel, D. Chretien, N. Kadhom, P. Edery, M. Lebideau, G. Dallner, A. Munnich, L. Ernster, P. Rustin, Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency, Lancet 356 (2000) 391–395.

[25] A. Thelin, S. Schedin, G. Dallner, Half-life of ubiquinone-9 in rat tissues, FEBS Lett. 313 (1992) 118–120.
[26] T. Nakamura, T. Ohno, K. Hamamura, T. Sato, Metabolism of coenzyme Q10: biliary and urinary excretion study in guinea pigs, Biofactors 9 (1999) 111–119.
[27] M. Bentinger, G. Dallner, T. Chojnacki, E. Swiezewska, Distribution and breakdown of labeled coenzyme Q10 in rat, Free Radic. Biol. Med. 34 (2003) 563–575.
[28] G.P. Littarru, L. Tiano, Clinical aspects of coenzyme Q10: an update, Curr. Opin. Clin. Nutr. Metab. Care 8 (2005) 641–646.
[29] P. Herpin, G. Lossec, I. Schmidt, F. Cohen-Adad, C. Duchamp, L. Lefaucheur, F. Goglia, A. Lanni, Effect of age and cold exposure on morphofunctional characteristics of skeletal muscle in neonatal pigs, Pflugers Arch. 444 (2002) 610–618.
[30] F. Navarro, P. Navas, J.R. Burgess, R.I. Bello, R. De Cabo, A. Arroyo, J.M. Villalba, Vitamin E and selenium deficiency induces expression of the ubiquinone-dependent antioxidant system at the plasma membrane, FASEB J. 12 (1998) 1665–1673.
[31] A. Kalen, E.L. Appelkvist, T. Chojnacki, G. Dallner, Nonaprenyl-4-hydroxybenzoate transferase, an enzyme involved in ubiquinone biosynthesis, in the endoplasmic reticulum–Golgi system of rat liver, J. Biol. Chem. 265 (1990) 1158–1164.
[32] H. Teclebrhan, J. Olsson, E. Swiezewska, G. Dallner, Biosynthesis of the side chain of ubiquinone:trans-prenyltransferase in rat liver microsomes, J. Biol. Chem. 268 (1993) 23081–23086.
[33] J. Mollet, A. Delahodde, V. Serre, D. Chretien, D. Schlemmer, A. Lombes, N. Boddaert, I. Desguerre, P. de Lonlay, H.O. de Baulny, A. Munnich, A. Rotig, CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures, Am. J. Hum. Genet. 82 (2008) 623–630.
[34] M. Bentinger, M. Turunen, X.X. Zhang, Y.J. Wan, G. Dallner, Involvement of retinoid X receptor alpha in coenzyme Q metabolism, J. Mol. Biol. 326 (2003) 795–803.
[35] M. Turunen, J.M. Peters, F.J. Gonzalez, S. Schedin, G. Dallner, Influence of peroxisome proliferator-activated receptor alpha on ubiquinone biosynthesis, J. Mol. Biol. 297 (2000) 607–614.
[36] Z. Guan, M. Soderberg, P. Sindelar, S.B. Prusiner, K. Kristensson, G. Dallner, Lipid composition in scrapie-infected mouse brain: prion infection increases the levels of dolichyl phosphate and ubiquinone, J. Neurochem. 66 (1996) 277–285.