Role of Coenzyme Q

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Coenzyme Q is a unique lipidic molecule highly conserved in evolution and essential to maintaining aerobic metabolism. It is endogenously synthesized in all cells by a very complex pathway involving a group of nuclear genes that share high homology among species. This pathway is tightly regulated at transcription and translation, but also by environment and energy requirements. Dysfunction in CoQ synthesis produces mitochondrial diseases that can partially reverted by CoQ supplementation. The main function of CoQ10 in human metabolism and antioxidant protection of membranes against oxidation and ferroptosis makes CoQ10 as an essential factor in many metabolic, chronic diseases and also in aging.

Keywords: coenzyme Q ; Age-Associated Metabolic Disorders ; aging ; mitochondria ; mitochondrial disease ; chronic disease

1. CoQ as Metabolic Integrative Factor for Cellular Homeostasis

The main function of CoQ is to act as an electron carrier in the ETC that drives all electrons to complex III. Most of the redaction reactions of CoQ come from NADH-dependent complex I and $FADH_2$-dependent complex II. However, CoQ is also reduced by diverse oxidoreductases, which represents key steps in important metabolic pathways, such as iron sulfur cluster synthesis, nucleotide synthesis, and sulfide metabolism [1][2]. These reactions and their metabolic mechanisms have been recently reviewed by [3].

As a ubiquitous component of eukaryotic lipid membranes, CoQ participates in electron transfer activities. In these redox activities, the redox state of CoQ determines where and how electrons move from the electron carrier and if leaks produce reactive oxygen species (ROS) [4]. Although free radicals have long been thought to be responsible for aging and age-related diseases, recent reports indicate that they have both positive and negative effects on longevity and health acting as integrators of cellular homeostasis [1][4][5][6]. The levels of CoQ, its redox state, and its interaction with CoQ-dependent enzymatic activities can be key in the modulation of cellular homeostasis.

1.1. Mitochondrial Redox Reactions

1.1.1. Redox Reactions at the ETC

The CoQ-dependent redox reactions in the mitochondria are linked directly or indirectly to oxidative phosphorylation (OXPHOS), in which electrons flow through mitochondrial complexes to generate the proton gradient necessary for ATP synthesis, until they finally reach oxygen to reduce it to water [1], additionally affecting diverse metabolic pathways [3].

To access ETC, the energy of the electron flows clusters the mitochondrial redox reactions into three groups, depending on their redox potential [7]. The more energetic dehydrogenases operate at approximately −280 mV and transfer electrons from metabolites to NAD^+, reducing it to NADH, and oxidizing the proper metabolite to another with lower potential energy. Within this group, enzymes, for amino acid metabolism, such as 2-oxoadipate dehydrogenase for lysine catabolism and branched-chain dehydrogenases for leucine, isoleucine and valine catabolism; hydroxyacyl-CoA-dehydrogenase for fatty-acid β-oxidation; pyruvate dehydrogenase for carbohydrate catabolism; and the three NAD-dehydrogenases integrated in the Krebs cycle: isocitrate dehydrogenase, 2-oxoglutarate dehydrogenase, and malate dehydrogenase are included. All these dehydrogenases produce NADH to feed mitochondrial complex I, which uses the energy to generate the proton gradient necessary for ATP synthesis and transfers the electrons to ubiquinone reducing it to ubiquinol, which is the substrate for complex III.

The second group of dehydrogenases operate at a lower redox potential of approximately +20 mV. They use FAD, a flavin-adenine dinucleotide that is reduced to $FADH_2$, and transfer electrons from metabolites directly to ubiquinone, without contribute to the proton gradient generation. This group includes succinate dehydrogenase (complex II), enzymes for amino acid metabolism, such as proline dehydrogenase, dihydroorotate dehydrogenase for pyrimidine nucleotide metabolism, acyl-CoA dehydrogenases for fatty-acid beta oxidation, and glycerol-3-phosphate dehydrogenase, which

shuttles the glycolytic electrons from NADH directly to the mitochondrial respiratory chain to regenerate NAD^+ and avoid the blockage of the glycolysis. All these dehydrogenases use as substrate CoQ producing ubiquinol, which is reoxidized by complex III, using this energy to generate the mitochondrial proton gradient, and finally transferring the electrons to molecules of cytochrome c [3].

The third group of dehydrogenases operate at a very low redox potential of approximately +320 mV. Here, the cytochrome c linked enzymes are included, such as the sulfite dehydrogenase necessary for cysteine catabolism, which oxidizes sulfite to sulfate and reduces cytochrome c. Finally, electrons from cytochrome c go through complex IV, contributing to the proton gradient, until they reach oxygen at +600 mV.

1.1.2. CoQ Role in Reactive Oxygen Species Balance

Eleven sites in the ETC that leak electrons to oxygen producing ROS have been associated with substrate oxidation and oxidative phosphorylation in mitochondria [8]. These sites are located inside the oxoacid dehydrogenases that feed electrons to NAD^+, but higher production has been recorded in proper mitochondrial complexes III, I, and II in the sites where CoQ presents its redox activity [7]. In addition, the rate of ROS production can vary depending on the tissue, showing higher production in brown adipose tissue compared with skeletal muscle, and being heart the organ with lower rates [9]. The type of substrate is also crucial, succinate is the metabolite that causes higher production of ROS, and both fatty acids and amino acids the metabolites that produces the lower levels [8]. Most of the hydrogen peroxide production takes place in complex I, while glycerol-3-phophate, fatty acids and glutamate/malate generate an equal amount in complexes I and III, and inside the proper glycerol-3-phosphate dehydrogenase. ROS is also produced by 2-oxoglutarate dehydrogenase.

Due to the topology of the mitochondria and the presence of a double membrane, these enzymes can generate superoxide either in the intermembrane space or in the matrix, but hydrogen peroxide exclusively in the matrix. The specific site of ROS production is important for redox signaling without generating catastrophic energetic effects [7]. Thus, we can distinguish intramitochondrial redox signaling, in which all targets are located inside mitochondria, and redox signaling from mitochondria to the rest of the cell (retrograde redox signaling). This ROS-dependent signaling process can even affect targets located outside cells. Among the targets affected by mitochondrial ROS are the initiation of hypoxia-inducible factor (HIF) signaling and its effect in gene expression modulation, insulin secretion stimulated by redox signaling due to the metabolism of branched-chain keto acids and fatty acids, retrograde redox signaling that modulates PGC1α during exercise in skeletal muscle, and the redox signaling that affects immune cells [10][11].

1.1.3. Mitochondrial CoQ Is Essential for Many Different Metabolic Processes

In addition to its known activity as a redox carrier among complexes I, II, and III of the ETC, CoQ also receives electrons from many different dehydrogenases [3][12][13]. CoQ receives electrons from mitochondrial glycerol-3-phosphate dehydrogenase (G3PDH) that connects glycolysis, OXPHOS, and fatty acid metabolism [14]. CoQ is also reduced by the electron-transport flavoprotein dehydrogenase (ETFDH), an essential enzyme in β-oxidation of fatty acids and in the oxidation of branched amino acids [15]. The capacity as an electron acceptor of CoQ is also essential for the activity of proline dehydrogenase (PROD), involved in glyoxylate metabolism [16], and sulphide-quinone oxidoreductase (SQR) that participates in sulphide detoxification [17], an important regulator of many cellular processes [18][19]. Further, CoQ is also reduced by choline dehydrogenase (CHDH) [20], from choline to glycine conversion, and dihydroorotate dehydrogenase (DHODH), from dihydro-orotate to orotate transformation, which is involved in pyridine nucleotide synthesis [21].

Further, CoQ also participates in the dissipation of energy from the ETC by the dissemination of the proton gradient as heat. CoQ associates to uncoupling proteins localized in the IMM playing in its regulation [22].

Moreover, it has recently been shown that the oxidation of ubiquinol by complex III of the ETC is an obligatory reaction to maintain tumor growth [23].

Another important aspect of the essential participation of CoQ in mitochondrial physiology is its role as a structural element in complexes I and III in the ETC [24][25]. In fact, CoQ is essential for the maintenance of the structure of complex III since the supplementation of yeast with CoQ restores the assembly of complex III in CoQ-deficient strains [26], and CoQ is also involved in complex I stability [27]. Interestingly, the deterioration of complexes I and III has been associated with the progression of different neurodegenerative diseases [28][29]. Further, defects of complexes downstream of the CoQ site end in the accumulation of ubiquinol in ETC that destabilizes complex I by ROS production, generating a vicious cycle [27].

CoQ is also a component of respirasome [30][31], and also participates in the assembly and the dynamics of supercomplexes [32]. Recently, it has been indicated that OPA1, a regulator of the fusion of the mitochondrial outer

membrane, mediates the regulation of complex IV activity through a CoQ-dependent procedure [33]. Interestingly, a pool of CoQ is associated with complex I + III + IV supercomplexes, whereas free CoQ is dedicated to complex II-dependent respiratory chain activity [34][35][36]. This is very important as supercomplexes are associated with a balanced ETC chain activity and point to the regulatory role of CoQ in their assembly dynamics [32][37][38]. CoQ is also importantly implicated in the dynamics of the assembly and stability of these supercomplexes involved in mitochondrial efficiency that, when altered, induce mitochondrial dysfunction-mediated metabolic diseases and aging [39][40].

Recently, another key function of CoQ in mitochondria has been found in the outer membrane [41]. MitoNEET, also known as CDGS1 iron sulfur domain 1 (CISD1) protein, is a redox-active and pH-sensing protein that regulates energy metabolism, iron homeostasis, and ROS in mitochondria. MitoNEET interacts with reduced flavin mononucleotide (FMNH2) that reduces mitoNEET sulfoferric [2Fe–2S] clusters, which are oxidized back with CoQ being the most efficient electron acceptor [1][19]. As one of the proteins repaired by MitoNEET is the iron-master regulator IRP-1, which limits iron access to mitochondria to protect against ferroptosis in high ROS production, CoQ can be considered as an important redox-sensing factor in the adaptive response against oxidative injury, and a key component in the prevention of ferroptosis caused by mitochondrial dysfunction [1].

Finally, it has been suggested that CoQ inhibits the calcium-dependent opening of the mitochondrial permeability transition pore (PTP) and modulates the mitochondrial uncoupling proteins (UCPs) [2].

1.2. Extramitochondrial Redox Reactions

Since the discovery that extramitochondrial ubiquinol possesses antioxidant functions, efforts have been made to characterize the physiological enzyme reduction systems. It has been widely described that CoQ and vitamin E inhibit lipid peroxidation by scavenging lipid peroxyl radicals, and that CoQ directly scavenges the perferryl radical, thereby preventing the initiation of lipid peroxidation [19][42].

These important functions require continuous regeneration of ubiquinol from the oxidized ubiquinone and different quinone reductases have been proposed. In this way, the cytosolic enzymes that reduce extramitochondrial ubiquinone can be grouped depending on their dependence on NADPH and NADH and if they have flavin adenine dinucleotide (FAD) as prosthetic group [42]. The highest rate of extramitochondrial ubiquinone reduction described is accomplished by flavoenzymes belonging to a unique family of pyridine nucleotide oxidoreductases, such as lipoamide dehydrogenase (LipDH), mammalian thioredoxin reductase (TrxR-1), and glutathione reductase (GR) [42]. LipDH reduces CoQ with either NADH or NADPH, works at acidic pH, and its activity depends on the presence of zinc. TrxR-1 is a selenoenzyme with very broad substrate specificity that has an optimal physiological pH of 7.5 and uses either NADPH or NADH, being the most efficient ubiquinone reductase so far tested. GR is a flavoenzyme, the activity of which is also stimulated by zinc, and has an acidic pH.

On the other hand, NAD(P)H:quinone acceptor oxidoreductase1 (NQO1) plays a central role in the processes of stress adaptation, including oxidative stress [4]. NQO1 and cytochrome b_5 reductase (CYTB5R3) regulate the stress adaptation response as a central component of the transplasma membrane redox system that is responsible for preventing lipid peroxidation by reducing oxidized antioxidants, such as vitamins E and C, and the proper CoQ [43][44]. An overexpression of these enzymes in mice improved health- and life-span by modulating lipid-mediated respiration [45][46][47]. CoQ is also involved in alterations in the redox environment by receiving highly energized electrons from NAD(P)H, and possibly in the local regulation of NAD(P)H-dependent enzymes, such as sirtuins acting as metabolic switch [48][49].

CoQ in plasma membrane contributes to prevent ferroptosis, as substrate of ferroptosis suppressor protein 1 (FSP1), acting in association to the glutathione-dependent lipid hydroperoxidase glutathione peroxidase 4 (GPX4) [50][51]. The relevant extramitochondrial redox reactions that depend on CoQ, which are integrated with other pathways, are essential to regulate cellular homeostasis and metabolism [19].

CoQ also plays an key antioxidant role in the prevention of oxidative damage in plasma cholesterol lipoproteins, essentially in low-density lipoproteins (LDLs) [52]. This role has been essentially considered in the prevention of, and protection against, cardiovascular diseases and atherogenesis [53][54]. Interestingly, a NADH-dependent reductase able to reduce LDL-associated CoQ has been found in the outer side of the plasma membrane of hepatocytes [55], possibly indicating a mechanism to maintain the redox cycle of CoQ in plasma. The importance of this enzyme in the maintenance of ubiquinol in plasma in aging and metabolic diseases is under study.

2. Role of CoQ in Aging and Age-Associated Metabolic Disorders

The accumulation of dysfunctional mitochondria is a shared feature of both aging and metabolic disorders [56][57][58][59]. Evidence indicating the essential role of mitochondrial physiology in the increasing dysfunction of tissues and organs during aging has been accumulating over the last few years [60][61]. This indicates that any therapy able to maintain a balanced mitochondrial turnover and dynamics can delay age-associated metabolic diseases and improve functionality during the progression of aging [48][53][1].

The essential role of CoQ in the maintenance of mitochondrial activities and in the prevention of oxidative damage in cells and plasma lipoproteins points to its importance in aging and in age-related diseases [48][62]. However, it is not clear if the decrease in CoQ levels associated with aging is the cause of mitochondrial dysfunction or a consequence of the deterioration of the turnover and dynamics of mitochondria found in metabolic diseases and aging [57][60][63].

We can consider that the secondary CoQ deficiency associated with aging may be a consequence of OXPHOS dysfunction [64]. Several CoQ biosynthesis genes were downregulated in mice showing impaired mtDNA gene expression [64]. Many components of the CoQ-synthome suffered a clear decrease in mitochondria: COQ3, COQ5, COQ6, COQ7, COQ8A/ADCK3, COQ9, and COQ10A. On the other hand, two of these enzymes (PDSS2 and COQ8B/ADCK4) increased, indicating a different response of the members of the synthome to mitochondrial dysfunction [64]. Additionally, COQ8A/ADCK3 and COQ8B/ADCK4 are regulated depending on the glycolytic or respiratory conditions, indicating a response to the metabolic conditions [65]. It has been recently reported that in glioma cells, the inhibition of CoQ biosynthesis is associated with the stabilization of HIF-1 and the switch toward glycolysis, introducing a mechanism in the regulation of the metabolism and the development of cancer [66].

The decrease in CoQ levels found in mutants and in aged animals could be a response to the equilibrium to maintain a balanced activity of the ETC. However, we cannot discard a side effect of OXPHOS dysfunction that affects activities in the inner mitochondrial membrane that regulate CoQ synthesis [29], and the transport of proteins into the mitochondrial matrix that can destabilize the CoQ-synthome [64].

Interestingly, the maintenance of balanced mitochondrial dynamics is essential to avoid mitochondrial dysfunction during aging and metabolic diseases [56]. The transport of polyprenyl pyrophosphate from endoplasmic reticulum to mitochondria is severely affected in mitofusin2 (MFN2) KO mice and causes CoQ deficiency [67]. MFN2 is directly involved in mitochondrial fusion [68], and also in the tethering of mitochondria to the ER [69]. Communication between the ER and mitochondria affects many physiological processes, and its alteration has been associated with aging [70] and many chronic pathologies associated with aging, such as neurodegenerative diseases, metabolic syndromes, and cancer [71].

On the other hand, a depletion in CoQ levels activates mitophagy [72] and increases the dysfunction of mitochondria associated with higher oxidative stress and apoptosis in cultured cells [73]. Further, a depletion in CoQ levels would not only add more disturbing factors for mitochondrial physiology, but also affects membrane antioxidant activities. This cycle would accelerate mitochondrial dysfunction while aggravating oxidative stress.

In support of the key role of CoQ in the delay of this vicious cycle, recent studies have proposed the therapeutic use of CoQ, or bioactive compounds able to increase its levels, to reduce the progression of age-related diseases and to improve healthy aging [1][74][75]. Treatments with ubiquinol can rescue statin-associated mitochondrial dysfunction and rhabdomyolysis, indicating that a depletion in CoQ levels in muscle causes mitochondrial dysfunction through the chronic use of statins [76]. Lower CoQ levels have been recently associated with the progress of chronic kidney diseases [77].

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