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Coenzyme Q homeostasis in aging: response to non-genetic interventions

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Abstract.

Coenzyme Q (CoQ) is a key component for many essential metabolic and antioxidant activities in cells in mitochondria and cell membranes. Mitochondrial dysfunction is one of the hallmarks of aging and age-related diseases. Deprivation of CoQ during aging can be the cause or the consequence of this mitochondrial dysfunction. In any case, it seems clear that aging-associated CoQ deprivation accelerates mitochondrial dysfunction in these diseases. Non-genetic prolongevity interventions, including CoQ dietary supplementation, can increase CoQ levels in mitochondria and cell membranes improving mitochondrial activity and delaying cell and tissue deterioration by oxidative damage. In this review, we discuss the importance of CoQ deprivation in aging and age-related diseases and the effect of prolongevity interventions on CoQ levels and synthesis and CoQ-dependent antioxidant activities.

Keywords:

Coenzyme Q; aging; age-related diseases; mitochondria; reactive oxygen species; oxidative damage; calorie restriction; polyphenols;

1. Introduction. Aging and CoQ homeostasis.

Many different theories have been coined to elucidate the degenerative processes that accompany aging [1]. One of them is the free radical theory of aging [2] that associate the unbalance in the production and elimination of reactive oxygen species (ROS) with the aging process. The increase of ROS levels or the decrease in antioxidant protection during aging cause damage in cell molecules and structures ending in the irreversible accumulation of damaged macromolecules [3]. Thus, the accumulation of damaged molecules generated by this unbalance together with an inefficient turnover system is considered the main cause of the general physiological dysfunction occurring during aging. On the contrary, healthy aging, in which the decay in the physiology of organs is slow, can be reached by the control of ROS production and the maintenance of a balanced antioxidant capacity [4].

In mitochondria, molecular oxygen is the final acceptor of electrons in the complex IV of the electron transport chain (mETC). During this process, some electrons escapes the mETC and react directly with molecular oxygen producing superoxide as primary ROS. At low concentrations, ROS modulate cell activities that control the synthesis and activity of antioxidant enzymes in a hormetic response [5]. The main antioxidant enzymes are superoxide dismutase (SOD) that converts superoxide to hydrogen peroxide, and catalase, peroxiredoxins and glutathione peroxidase (GPx) that eliminates hydrogen peroxide producing water. Cells also contains antioxidant molecules such as ascorbic acid, α-tocopherol, glutathione or coenzyme Q_{10} (CoQ_{10} , ubiquinone for its oxidized form and ubiquinol for its reduced form) that are used by these enzymes and others such as cytochrome b_5 reductase ($CytB_5R_3$) or NAD(P)H quinone dehydrogenase 1 (NQO1) to protect macromolecules, mainly lipids, against oxidative damage. Under conditions of mitochondrial dysfunction, production of ROS increases, surpass the capacity of the antioxidant system to scavenge ROS and causes the accumulation of damaged components including lipids, proteins and DNA.

Currently, it seems clear that aging is accompanied by the accumulation of dysfunctional mitochondria in cells and tissues [6-8]. Many age-related physiological dysfunctions and diseases such as sarcopenia, type 2 diabetes, neurodegeneration, cardiovascular disease, liver and kidney dysfunctions,

chronic inflammation, stem cell deterioration, vascular damage and cancer are accompanied by the accumulation of dysfunctional mitochondria [7, 9-17]. Dysfunctional mitochondria is not only responsible of high production of ROS but also affect Ca^{2+} homeostasis, synthesis of nucleotides and phospholipids, apoptosis and deteriorated immune response [18, 19].

CoQ_{10} is a vital factor for mitochondrial activity in which its main function is to transport electrons through the mitochondrial respiratory chain from complexes I and II to complex III [20] and also to stabilize and control the assembling in supercomplexes [21, 22]. Moreover, mitochondrial CoQ also plays many other essential functions in mitochondria including the synthesis of many compounds and the metabolism of sugars, lipids and aminoacids [23]. Because its essential role in mitochondrial physiology, decrease of CoQ_{10} levels can be responsible or, at least, contribute to the acceleration of the dysfunction of mitochondrial activity associated with aging and age-related diseases [24].

CoQ is also a potent antioxidant in cell membranes and in plasma lipoproteins. CoQ protects lipids, proteins and nucleic acids from oxidative damage [25, 26]. The reduced form of CoQ, ubiquinol, prevents both, the initiation and propagation of lipid peroxidation in cell membranes [26, 27] but also in plasma lipoproteins [28]. Furthermore, CoQ plays a central activity as antioxidant in membranes regenerating other main antioxidants such as α-tocopherol or ascorbic acid [29]. This antioxidant activity is maintained by cell dehydrogenases that transfer electrons from NAD(P)H to oxidized ubiquinone. In cells, two main dehydrogenases have been found: $CytB_5R_3$ [30] and NQO1 [31]. In the case of plasma lipoproteins, a dehydrogenase located at the outer surface of plasma membrane from hepatocytes has been recently associated with the maintenance of the high reduced/oxidized ratios found in plasma [32].

CoQ also regulates gene expression [33]. Interestingly, many of the genes regulated are related with the inflammatory response [34, 35] and can show anti-inflammatory properties [19]. Further, the activities of CoQ-dependent antioxidant enzymes in cell membranes [36, 37] or in mitochondria [38, 39] are also important in the regulation of apoptosis that can explain the high ratio of apoptosis found in CoQ_{10}-depleted cells [40], such as neurons [41], retina [42], kidney [43], ischemia-reperfusion damaged tissues [44] or ovocites [45] (Figure 1).

For all these reasons, depletion of CoQ_{10} during aging may be considered a key factor in the loss of function of many tissues and organs and a biomarker of accelerated aging. Here I review the actual knowledge about the importance of maintaining the homeostasis of CoQ_{10} during aging and the influence of known prolongevity non-genetic interventions in CoQ_{10} synthesis and levels.

2. Pleiotropic functions of CoQ.

2.1. Mitochondrial functions.

It is widely known that CoQ is an essential factor in the transport of electron from complexes I and II to complex III in the inner mitochondrial membrane [46]. Further, CoQ is essential for the assembly of complex III in yeast [47]. Although it has been long time considered that different CoQ pools are present in mitochondria, one linked to proteins and other free in the membrane, CoQ is also essential for the assembly of individual complexes, especially I, III and IV, into supercomplexes [48]. In fact, recent studies indicate that CoQ is essential in the structure of mitochondrial supercomplexes [21, 49]. Formation of supercomplexes permits a more efficient electron transfer through the individual complexes [48], reduces the production of ROS and permits a more balanced activity of the mitochondrial electron transport chain. Interestingly, in rat heart, supercomplexes show a decline during aging [50] and this destabilization causes lower oxidative capacity and is responsible of a higher superoxide production [51]. The role of CoQ_{10} depletion in this destabilization remains to be determined, although likely contributes to the age-related deterioration.

In mitochondria, CoQ not only receives electrons from complexes I and II of the mETC, it is also the electron acceptor of other dehydrogenases involved in many different and essential processes such as: dihydroorotate dehydrogenase involved in pyrimidine biosynthesis [52]; mitochondrial glycerol-3-phosphate dehydrogenase that connects glycolysis with oxidative phosphorylation and fatty acid metabolism [53, 54]; the electron transport flavoprotein dehydrogenase, key enzyme involved in fatty acid β-oxidation and the catabolism of branched-chain amino acids [55]; proline dehydrogenase, involved in the proline and arginine metabolism [56]; and sulfide-quinone oxidoreductase, involved in sulfide detoxification [57]. Ubiquinol, the reduced form of CoQ, generated by all these

processes, is reoxidized back to ubiquinone by complex III in the mETC contributing to the generation of the proton motile force used to synthesize ATP.

Recently, another key function of CoQ in mitochondria has been found in the outer membrane. MitoNEET, also known 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 [58]. MitoNEET null mitochondria from mouse cardiomyocytes shows reduced oxidative capacity indicating the importance of this enzyme in the regulation of mitochondrial respiration [59]. Its absence generates dysfunctional mitochondria that has been associated with the development of neurodegenerative diseases [60]. MitoNEET interacts with reduced Flavin mononucleotide ($FMNH_2$) that reduces mitoNEET sulfoferric [2Fe-2S] clusters. Reduced mitoNEET is oxidized back and ubiquinone has been recently considered the most efficient electron acceptor [61, 62]. Importantly, only the oxidized state of the mitoNEET cluster permits its transfer to a generic acceptor protein indicating the importance of CoQ in this process [63]. One of the proteins repaired by MitoNEET is the iron-master regulator IRP-1 [64] that, limiting iron access to mitochondria, can protect against ferroptosis in high ROS production situations [65, 66]. This converts mitoNEET in a CoQ-dependent redox sensing factor important in the adaptive response against oxidative injury [63] and ubiquinone in a key component in the prevention of ferroptosis caused by mitochondrial dysfunction. The importance of age-associated CoQ_{10} depletion in its activity remains to be clarified but I can hypothesize that it is important in the impairment of the capacity of cells to recover after oxidative damage.

Mitochondrial CoQ is also involved in the turnover of damaged mitochondria through the modulation of mito/autophagy. Deficiency in CoQ_{10} induces the degradation of mitochondria by mitophagy [67] and can aggravate the pathophysiology found in CoQ_{10} deficiency patients [68, 69]. Moreover, degradation rates of mitochondria are accelerated during aging [70] and this can contribute to the increase in the release of mitochondria-containing extracellular vesicle found in older adults with physical frailty and sarcopenia contributing to chronic inflammation [71]. Further, treatment with CoQ_{10} prevents mitophagy caused by pharmacological agents [72] and the use of analogues of CoQ such

as MitoQ, mitochondria-targeted antioxidant Q, prevents apoptosis and restores defective mitophagy in diabetic kidney cells [73]. I can then postulate that maintenance of balanced levels of CoQ_{10} in mitochondria can contribute to the control of the mitochondrial turnover rate that is accelerated during aging blocking premature senescence [74].

2.2. Cell membrane CoQ_{10}, the forgotten key function.

Although the role of CoQ in mitochondrial function is the principal matter of the scientific literature, CoQ is also present in all cell membranes and in plasma lipoproteins in which it plays a central role in the antioxidant system that prevents oxidative damage. Many of the age-related studies with CoQ supplementation focus in its antioxidant role and in the prevention of this oxidative damage [27]. In this system, CoQ protects phospholipids against oxidative damage directly by disrupting lipid peroxidation chain [75], or through maintaining α-tocopherol or ascorbic acid in their respective reduced and active state [76] or avoiding α-tocopherol consumption during peroxidation [77]. To exert its antioxidant activity, CoQ must be maintained in a redox cycle in which ubiquinone is reduced by reductases that transfer electrons from cytosolic NAD(P)H. Among these reductases, $CytB_5R_3$ [30, 78] and NQO1 [79], known as plasma membrane redox system (PMRS) are the most important enzymes that maintain ubiquinol levels in cell membranes [80]. Activation of these reductases produce the local accumulation of NAD^+ and then, the modulation of many critical biological activities associated with aging such as sirtuins [81] or the modulation of cell signaling pathways such as cyclic AMP (cAMP) [82].

The antioxidant function of CoQ is also important to prevent lipid peroxidation in mitochondrial membranes. CoQ inhibits lipid peroxidation in mitochondrial membranes depleted of α-tocopherol [83] and mETC-dependent lipid peroxidation is controlled by the concentration of reduced ubiquinone [84]. Importantly, CoQ_{10} is able to react rapidly with superoxide, contributing to the direct scavenging of this ROS and preventing progression to hydrogen peroxides [26]. As in the rest of membranes, the redox cycle of CoQ, maintained in mitochondria by mETC, is also responsible of the preservation of α-tocopherol and the prevention of the accumulation of oxidative damage [85]. Conservation of this antioxidant protection has been associated with the protection of cells

against mitochondrial but not receptor-mediated apoptosis [86]. It seems clear that ubiquinol at mitochondrial membranes is also a main compound in scavenging radicals to prevent lipid peroxidation produced by mitochondrial activity.

Massive production of superoxide both intracellularly by mitochondria or intracellular redox activities or extracellularly by NADPH oxidases found in inflammatory cells can produce cell damage that is avoided by the tandem CoQ/α-tocopherol in cell membranes [87] indicating the importance of this membrane-associated antioxidant system in apoptosis inhibition. Further, under stress conditions, CoQ_{10} in cell membranes also prevents the activation of apoptotic signaling mediated by the release of ceramides [88] and the activation of caspase-3 [76]. In this role, CoQ_{10} acts in combination with known antioxidants such as α-tocopherol or ascorbate [36].

Ferroptosis is a recent discover iron-dependent form of non-apoptotic cell death triggered by the accumulation of membrane lipid peroxidation products [89]. Then, reduction of lipid peroxidation by CoQ-dependent antioxidant function can reduce this cell death mechanism. Furthermore, recently, the CoQ oxidoreductase ferroptosis suppressor protein 1 (FSP1) has been shown to inhibit ferroptosis in parallel to glultathione peroxidase 4 [90]. Interestingly, FSP1 was formerly known as a flavoprotein called apoptosis-inducing factor mitochondria-associated 2 (AIFM2) [91]. It has been recently proposed that FSP1 blocks apoptosis by migrating from mitochondria to cell membrane and reducing plasma membrane CoQ_{10} using NAD(P)H [91], although ubiquinol-independent mechanisms have been also proposed [92]. Interestingly, ferroptosis has been associated with neurodegenerative diseases such as Parkinson's [93] or Alzheimer's [94] diseases, frailty [95], inflammation and cancer [96] and its prevention by CoQ_{10} could improve age-related diseases progression during aging (Figure 2).

2.3. Plasma low density lipoprotein (LDL) protection.

The importance of CoQ_{10} in the prevention of oxidative damage in plasma lipoproteins has been clearly demonstrated [28, 97]. Oxidative susceptibility of LDLs strongly depends on the levels of ubiquinol and α-tocopherol [97], although it is known that in plasma lipoproteins, ubiquinol is much more efficient in

inhibiting LDL oxidation than other antioxidants such as lycopene, β-carotene or α-tocopherol [28]. In experiments of oxidation performed in vitro with lipophilic peroxyl radical generators, the consumption of small molecular weight, non-proteinaceous antioxidants, demonstrate that the first antioxidant depleted was ubiquinol, followed by ascorbate, bilirubin, α-tocopherol, β-carotene and urate [98]. Other studies have also demonstrated that ubiquinol content in LDLs is the key factor influencing LDL susceptibility to oxidation [99]. Remarkably, the type of LDL capable of inducing the accumulation of cholesteryl esters in cells of the human aortic intima and originate atherosclerosis, known as multiple-modified low density lipoproteins [100], show high levels of oxidized CoQ_{10} and lower concentration of α-tocopherol [101] indicating a low capacity to preventing lipid peroxidation.

Dietary supplementation with CoQ_{10} increases the levels of ubiquinol in LDLs and increases the resistance of these lipoproteins against initiation of lipid peroxidation [102]. In very low density lipoproteins (VLDL) particles, ubiquinol is present in low amounts but provides a highly efficient antioxidant protection [103]. Another interesting aspect of CoQ_{10} is a reduction of the levels of LDLs in plasma introducing another antiatherogenic aspect.

Decrease of CoQ_{10} and ubiquinol levels in plasma has been considered a biomarker of aging [104]. Recently, the existence of a new NADH-oxidoreductase located at the outer surface of hepatocytes responsible of maintenance of reduced levels of CoQ_{10} in plasma has been reported [32]. Other plasma factors such as dihydrolipoic acid were considered as putative reducing agents for CoQ_{10} in LDLs [105]. It seems then clear that a right CoQ_{10} status in blood plasma is essential for the prevention of oxidative damage in LDLs and the reduction of the risk of cardiovascular disease during aging.

3.- **Regulation of COQ synthesis and mitochondrial dysfunction, a complex system.**

CoQ synthesis is performed in many steps driven by a complex of proteins encoded by nuclear genes (COQs genes) and located in the mitochondria (for an extended revision see [20]). Although it has been also proposed that synthesis of CoQ_{10} occurs in other organelles such as Golgi apparatus [106], nowadays, it is clear that CoQ_{10} is synthesized in the inner membrane of mitochondria [107] and

distributed to the rest of cell membranes through the endomembrane system [108].

The relationship of the regulation of COQs gene transcription and protein level with mitochondrial dysfunction is complex. In five model of mtDNA mutations that generate severe mitochondrial dysfunction many of the nuclear encoded mitochondrial genes were induced, but on the contrary, many of COQs genes suffered a strong reduction of expression [109]. COQ3, COQ5, COQ6, COQ7, COQ8A/aarF domain containing kinase (ADCK)3, COQ9 and COQ10A showed an important decrease whereas, prenyl-dihosphate synthase subunit 2 (PDSS2) and COQ8B/ADCK4 showed a clear increase indicating a different mechanism of regulation at the protein level [109]. This was accompanied by significant reductions of the levels of CoQ_9 and CoQ_{10} in these mutants.

The different response of COQ8A/ADCK3 and COQ8B/ADCK4 to mitochondrial dysfunction could be a consequence of their different role in the regulation of CoQ levels depending on the glycolytic or respiratory conditions of the organism [110]. The secondary CoQ deficiency associated with mtDNA mutation seems to depend on mitochondrial defective synthesis instead of cytosolic mevalonate pathway deficiency [109]. The downregulation of COQ proteins in response to mtDNA damage can be in response to the reduction of the activity of the oxidative phosphorylation (OXPHOS) system but also to the defects in the inner mitochondrial membrane that also affects the assembly of the CoQ-biosynthesis system. In this response, COQ8A/ADCK3 and COQ8B/ADCK4 can play regulatory roles to adapt CoQ biosynthesis to mitochondrial function and metabolic requirements [109]. COQ8A/ADCK3 plays important regulatory functions probably by acting as a mitochondrial kinase [111] with complex and unclear regulatory mechanisms [112] but with a key role in the stabilization of the CoQ biosynthesis complex [113].

Members of the CoQ-synthome need to be processed by proteolysis to be stabilized in the biosynthesis complex. The mitochondrial matrix octapeptidase Oct1p directly processes the N terminus of COQ5 improving its stability [114]. Further, we have recently found that the intramembrane rhomboid protease presenilin associated, rhomboid like (PARL), involved in Leigh-like syndrome, is needed for CoQ synthesis by processing COQ4 [115]. $PARL^{-/-}$ cells show also a

reduction in the levels of COQ3, COQ4, COQ5, COQ6, COQ7 and COQ9 indicating a key role in the stability of the complex of synthesis [115].

Mitochondrial dynamics, determined by the equilibrium between fission and fusion, can also be involved in the regulation of CoQ levels. Lack of mitofusin 2 (MFN2), a mitochondrial outer membrane protein involved in mitochondrial fusion [116] and in the tethering of mitochondria to endoplasmic reticulum (ER) [117] causes CoQ deficiency, probably by affecting the transfer of mevalonate precursors of CoQ tail from ER to mitochondria [118]. Interestingly, very recently it has been demonstrated that mitochondrial CoQ biosynthesis domains containing clusters of CoQ-synthesis complexes are enriched adjacent to the ER-mitochondria contact sites [119] indicating that maintenance of these contact sites during aging can be essential for the right synthesis ratio of CoQ.

To this complex scenario, I have to introduce a posttranscriptional control of the mean life of the mRNA of COQ7 that is controlled by the embryonic lethal, abnormal vision-like 1/ Hu antigen R (ELAV/HuR) [120]. The control of the lifespan of mRNA for COQ proteins can permit the coordination of CoQ synthesis with the biogenesis of OXPHOS protein complexes. This regulation probably respond to the ratio of the components of the synthome as has been demonstrated by the fact that some members can accumulate and, then, disturb the balance of the synthome, affecting synthesis [121]. Pumilio homology domain family member 3 (Puf3p), a RNA-binding protein located at the outer membrane of mitochondria, controls the lifespan of many nuclear-encoded mitochondrial proteins [121]. Puf3p regulates the abundance of COQ5 preventing the accumulation of this protein and enabling efficient CoQ synthesis in mitochondria [121]. Regulation through these RNA-binding proteins will explain the response of the mRNA of these genes to aging [122] and nutritional stress [123].

All these studies demonstrate a complex system of regulation of CoQ synthesis in mitochondria in which posttranscriptional and posttranslational regulatory processes play an essential role. The study of the relationship of these regulatory mechanisms and the levels of mRNA transcripts and proteins of the CoQ-synthome can clarify the importance of these levels in aging and age-related diseases.

4. Longevity and COQ-synthome.

The relationship of the protein levels of the COQ-synthome and longevity is conflicting. Timing protein clk-1 homolog (Clk-1)/COQ7 was early identified as a gene involved in longevity in the worm *C. elegans* [124]. In these worms, mutations in this gene result the slowing of several developmental and physiological processes affecting cell cycle, embryogenesis, postembryonic growth, behavior and aging. In these mutants, mitochondria was slightly impaired, and overexpression of Clk-1 gene accelerates physiological activities but, on the other hand, reduced life span [124].

On the other hand, reduction in the levels of mCLK-1(COQ7) in mice also produced a prolongevity effect without affecting $CoQ_9/_{10}$ levels [125] probably indicating that the effect was not associated with the amount of CoQ but with other probable effects related with the activityof the protein in mitochondria. These results suggest that the levels of Clk-1/COQ7 can affect other activities in mitochondria. In fact, young mClk-1($^{+/-}$) mutants show reduction of ETC activity, ATP synthesis and NAD^+ pool size. At the same time, these mutants also show increased levels of mitochondrial ROS but accompanied by a reduction of oxidative damage in cytosolic proteins probably by an increase in antioxidant system induced by a ROS-derived hormetic response [125]. Further, high ROS production by mitochondria is also responsible of the induction of the expression of hypoxia inducible factor-α (HIF-1α) and the elevated expression of inflammatory cytokines such as tumor necrosis factor-α (TNFα), a hallmark of immunosenescence [126]. The question arises, how decrease in the levels of ClK-1 affects mitochondrial activity in such a way? Is this decrease in older animals accelerating dysfunction of mitochondria during older ages increasing damage and inflammation?

In our studies, reduction of endogenous synthesized CoQ_9 in worms ended in greater longevity and reduction of superoxide production. However, feeding with CoQ_8-containing *E. coli* strains reduced life-span, indicating that the incorporation of rare forms of CoQ can interfere in longevity [127]. Interestingly, this same interfering effect was found when human cells were cultured with CoQ_6, the predominant form in yeast [128]. These cells showed higher ROS production and lower mitochondrial activity than cells cultured with CoQ_{10}. Other experiments performed in the short life-span mev-1 strain of *C. elegans* demonstrated a

prolongevity effect of CoQ_{10} supplementation through reducing oxidative stress highlighting the importance of the prevention of oxidative damage as key role of CoQ in longevity in these animals [129]. However, the prolongevity effect of CoQ reduction in *C. elegans* present some developmental problems. Absence of CoQ in coq-1, -2 or -8 mutants lead to larval developmental arrest without affecting embryo development [130]. All these studies indicate that severe CoQ deficit ended in a lethal phenotype and that reduction of CoQ levels in *C. elegans* can produce longer lifespan but probably by delaying development.

To respond to the puzzling effect of partial CLK-1 expression, the presence of CLK-1 in the nucleus was suggested in human cultured cells [131] although it was not found in worms [132]. The function of nuclear CLK-1 has been associated with the regulation of the response to metabolic metabolism requirements [131]. However, supplementation with CoQ in *clk-1* null mutants demonstrate that the loss of CoQ is the responsible of many of the effects found in these mutants including longevity [132]. However, this loss was only minor and specially in mice [125]. Although it has been alleged that a nuclear form of CLK-1 can be responsible of the prolongevity effect of reduction of CLK-1 levels in mice [131], other studies indicate that is the repression of the mRNA translation in cytoplasm the key factor in longevity [133]. Interestingly, in worms, mutations in Clk-1(qm30) produce a reduction in the efficiency of translation of genes involved in translation machinery but an increase in the translation of mRNA coding for oxidative phosphorylation and autophagy pathways [133] indicating a putative effect on the regulation of transcription of OXPHOS-related proteins.

Beside all these conflicting results, evidence indicates that maintenance of the levels of CoQ is needed for survival and longevity. In a mice model in which CoQ synthesis can be interrupted and restored at will, loss of CoQ leads to gradual loss of mitochondrial function and increase in disease and shortening of lifespan [134]. It has been proposed that depletion of CoQ does not acutely impair organ function and that addition of CoQ_{10} can improve mitochondrial function [134], however in this study KO of mCLK1 did not produce a complete elimination of CoQ_9 and CoQ_{10} in heart and other organs and CoQ_{10} supplementation did not increase CoQ_{10} levels in heart, muscle and kidney [134]. Another clk-1-deficient mice [135] rescued with the mouse clk-1 transgene (Tg96/l) shows higher

longevity but maintaining the equivalent amounts of CoQ than wild type animals [136]. However, at the same time, these animals showed reduced mitochondrial VO_2 and ATP content in comparison with wild-type animals indicating that reduction of mitochondrial activity can delay aging progression [136]. On the other hand, in the senescence-accelerated mouse prone (SAMP)1 mice model of accelerated senescence, supplementation with CoQ_{10} decelerates the characteristics of senescence and improve functional activity of many organs [137-140].

On the other hand, reduction of the levels of CoQ-synthome proteins has been associated with an increase in lifespan in mice [141] probably indicating a balanced control of protein levels to maintain a balanced activity of mitochondria during aging [114]. The reduction of the levels of CoQ-synthome members during aging can respond to an adaptive response to aging and mitochondrial dysfunction. Reduction of their levels have be associated with the increase of lifespan but without evidence of any effect in hepatic mitohormesis [141]. These evidence introduce a paradox in the role of CoQ in aging since, decrease of the expression and protein levels of some of the members of the complex of synthesis are associated with longevity but, at the same time, supplementation with exogenous CoQ_{10} improves many age-associated diseases and increase longevity [142]. In any case, CoQ could extend longevity through modulating endogenous stress signaling and downregulating protein synthesis [133, 143].

Probably we are focusing the discussion on levels and not on thresholds. It is probable that the equilibrium between CoQ levels and mitochondrial function is key to maintain a balanced mitochondrial activity, produce the levels of ROS necessary to keep a hormetic response and maintain antioxidant system active and to permit a right turnover of damaged mitochondria controlling biogenesis and mito/autophagy. The level of ROS undoubtedly can signalize different pathways in a hormetic response. It seems that is the equilibrium between ROS levels and oxidative damage the fact that determines the degree of oxidative damage and that ROS production increases with aging. Nevertheless, how much is adequate? Are we introducing disturbances in some organs but not in other by supplementing too much with CoQ_{10}?

6. Importance of CoQ depletion in aging and age-related diseases.

Due to the importance of CoQ_{10} in the maintenance of mitochondrial activities and in the prevention of oxidative damage in cells and in plasma lipoproteins an important question arises, is CoQ_{10} an essential factor in aging progression and in age-related diseases? We tried to answer this question some years ago with a focused review [24]. From this review, many other studies have demonstrated that maintenance of CoQ_{10} levels in elderly people are essential in the prevention or delay of many age-related dysfunctions.

From late eighties, the levels of CoQ in tissues during aging is a matter of controversy. From Kalen's group publication in 1989 [144], it is assumed that CoQ levels decrease in many tissues and organs during aging in both, animal models and humans. A age-dependent decline of levels of CoQ_9 in rats and CoQ_{10} in humans relating to tissues and organs wet weight was found [144]. Probably, this measurement can explain some minor discrepancies found in other studies that used protein levels as reference [145]. In any case, it seems clear that the levels of CoQ_{10} in human tissues decrease in late aging (77-81 years) in comparison with the levels found in young and mature people. This effect was found in most of the organs: lung, heart, spleen, liver, kidney, pancreas and adrenal [144]. In the case of brain, the evolution of CoQ during aging is conflicting since some studies indicated a decrease [146], whereas others show no changes once the levels reach a stable concentration in young organisms [145, 147]. If this decrease is associated with dysfunction of the members of the CoQ-synthome or a consequence of mitochondrial dysfunction remains to be clarified.

Aging is accompanied by the accumulation of dysfunctional mitochondria in cells and tissues. This accumulation is produced either by increase of the ratio of oxidative stress or by reduction of mito/authophagy processes. To this mitochondrial dysfunction, up-regulation of mitochondrial biogenesis, the induction of mitochondrial proteases and chaperones –as reponse to mitochondrial unfolded protein response (mUPR)– and adaptations of energy metabolism can be induced as compensatory adaptive mechanisms [148]. In general, it is widely assumed that mitochondrial function declines during mammalian aging accompanied by the accumulation of mutated mtDNA [149] that impairs the expression of mtDNA genes [150] that further aggravates the malfunction of mitochondria in a vicious cycle.

Through its relationship with mitochondrial dysfunction, deficiency of CoQ has been associated with many age-related diseases [151] such as type 2 diabetes or insulin resistance [152], cardiovascular disease [153], neurodegeneration [154], chronic kidney disease [155], liver disease [156], inflammaging and immunosenescence [157] or sarcopenia [158].

I can thus consider that secondary CoQ deficiency found in aging develops in response to the OXPHOS dysfunction [109]. On the contrary OXPHOS deficiency can cause CoQ decrease in five different conditional knock-out mouse strains with impaired mtDNA gene expression affecting replication, mtDNA maintenance, transcription, stabilization of RNA and translation, low levels of CoQ_9 were also found [109]. All these mutants show cardiomyopathy and very short lifespan in comparison with wild type animals. In these animals, many components of the CoQ-synthome show a clear decrease in mitochondria [109]. These results suggest the following questions, is mitochondrial dysfunction driving CoQ decrease or the decrease in CoQ originates mitochondrial dysfunction? Is the decrease of CoQ levels in these mutants a mechanism to adjust these levels to the activity of the mETC or is only a response to mitochondrial dysfunctions associated with the homeostasis of mitochondria? Probably, the loss of OXPHOS activity is affecting the structure of the inner mitochondrial membrane destabilizing the CoQ-synthome as proposed recenty by Kühl and collaborators [109].

The importance of CoQ deficiency during aging shows paradoxical aspects since some studies have shown that defects in the CoQ-synthome produce increase in lifespan in an effect attributed to mitohormesis and the increase of mitophagy and mitochondrial turnover [142] although in other cases this effect has been not attributed to the induction of mitohormesis, at least, in liver [141]. Probably, in these cases, the association of moderate CoQ deficiency with the induction of mitophagy will help to remove dysfunctional mitochondria improving by this mechanism cell metabolism and reducing oxidative damage. However, when disruption of the mito/autophagy mechanisms coincide with a decrease of CoQ synthesis, the result could be the acceleration in the accumulation of damaged mitochondria impairing age-dependent dysfunction.

6.1. The statins issue.

Statins are widely used to decrease cholesterol synthesis in the treatment of hypercholesterolemia affecting many aged individuals. The large use of these compounds in aged population have trigger their discontinuation in older adults in the context of declining health status due to their secondary effects [159]. Cholesterol and CoQ isoprene tail shares the initial steps of synthesis. Through inhibiting 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase, one of the initial enzymes in the cholesterol synthesis pathway, statins can also affect the synthesis of dolichol and CoQ_{10} and the isoprenylation of many proteins [160]. For this reason, the use of statins can affect CoQ synthesis and accelerate the decrease of CoQ in human tissues in elderly people. This aspect is controversial since the balance between the protective effect of statins in the prevention of cardiovascular disease and the side-effects associated with mitochondrial dysfunction probably produced by CoQ depletion are a matter of controversy. The side effects such as chronic-statin dependent muscle disorders [161] are especially important in a population that shows muscle debility and sarcopenia such as in aged people. I can consider that due to the chronic use of statins to decrease cholesterol levels mainly in aged people, the side effect affecting CoQ_{10} levels can produce several damaging effects in muscle, brain and cardiovascular tissues. In fact, cardiomyopathy associated with the chronic use of statins respond to the withdrawal of these drugs and the administration of CoQ_{10} [162].

Statins seem to produce clear effects on muscle. Initial studies indicated that statins could reduce the mitochondrial function in muscle accelerating the decline of mitochondrial activities [163]. In patient treated with simvastatin, a decrease in muscle OXPHOS activity and increase in insulin intolerance was reported produced by the decrease in the amount of CoQ_{10} [164]. In preclinical studies, the statin-induced myotoxicity was exacerbated by aging, probably by the previous CoQ deficiency found in aged organisms [165]. Further, experiments performed in human dermal fibroblasts demonstrate that CoQ_{10} levels decrease after statin treatment driving mitochondrial permeability transition and bioenergetics dysfunction that can generate premature aging [166]. Despite the studies reported to date, the effect of statins and the putative protective effect of CoQ_{10} supplementation is under debate. Some studies indicate that statins affect mitochondrial activity but does not affect CoQ levels [167].

The safety of CoQ_{10} treatment permits to be tested in patients requiring statin treatment to reduce myopathic complains associated with chronic statin treatment [168]. The design of clear clinical trials are needed although preclinical studies in animals indicate that statins induce mitochondrial dysfunction in muscle and that CoQ_{10} treatment reverts these effects and improves exercise tolerance [169]. Reduction of CoQ_{10} levels in muscle could also explain muscle pain and exercise intolerance found in some statin-treated patients. In fact, treatment with ubiquinol, rescued simvastatin suppression of mitochondrial physiology in human rhabdomyosarcoma cells indicating that reduction of CoQ_{10} levels in muscle wass the main factor in the deterioration of mitochondrial function caused by these treatments [170]. Moreover, a recent clinical trial demonstrates that subclinical mitochondrial dysfunction induced by 8 week of treatment with simvastatin in muscle of healthy subjects can be reversed by the treatment with ubiquinol [171]. However, the low bioavailability of supplemented CoQ_{10} in some organs, such as muscle, kidney or brain, can be taken into consideration since a lack of effect by CoQ_{10} treatment can be due to the low uptake of these organs [172] This can explain the null improvement produced by CoQ_{10} supplementation in statin-treated patients [173, 174]. Strategies to increase CoQ_{10} access to these organs will help to prevent mitochondrial dysfunction produced by chronic statin treatment especially in muscle, heart and brain.

In the case of central nervous system, the effect of statins is not clear. In response to the consumers concerns about the treatment with statins and a high risk of memory decline, Samaras et al., have recently published an observational study concluding that in community-dwelling elderly Australians no correlation between statin treatment and memory decline can be found [175]. However, in other studies trying to relate statin therapy with improvement of Alzheimer's disease progression, worse white matter integrity was found in statin-treated individuals [176]. On the other hand, animal studies have shown reduction of the levels of CoQ_{10} in brain associated with the impairment of cognitive function [177]. Probably the treatment with statins unable to reach central nervous system will reduce a putative cognitive dysfunction associated with CoQ_{10} decrease in brain [178].

Although statins are used to prevent cardiovascular disease associated with high cholesterol, the decrease in CoQ_{10} levels in plasma can produce damaging effects. Studies performed with patients treated with pravastatin or cerivastatin during 6 months showed an increase in the oxidation levels of LDLs that were reversed by supplementation with 60 mg/day of CoQ_{10} [179]. Combination of statin treatment with the anti-hyperlipidemic drug increased LDL oxidation that was also reversed by CoQ_{10} [180]. Prevention of LDL oxidation is important not only to reduce atherosclerosis but also to prevent chronic inflammation since in healthy man, levels of CoQ in LDLs negatively correlate with the presence of soluble CD40, a marker of inflammation [181].

In general, it seems clear that supplementation with CoQ_{10} is important to maintain its levels in statin-treated patients. This is supported by many studies that indicated that supplementation with CoQ_{10} together with statin treatment can reduce side effects due to the depletion of CoQ_{10} [179, 182-184].

7. Non-genetic interventions that maintain CoQ_{10} homeostasis during aging.

The role of CoQ in aging and longevity has been studied in many model organisms from yeast to humans and its depletion has been associated with the mitochondrial dysfunction associated with cardiovascular, kidney, metabolic and lung diseases [185], metabolic syndrome, neurodegenerative diseases, immunosenescence or fertility and reproduction [186]. The importance of CoQ_{10} in aging is highlighted by the improvement found in many organs and systems after supplementation in the treatment of aging-related diseases [186].

Following, I show the effects of supplementation with CoQ and different prolongevity procedures in the homeostasis of CoQ in mitochondria during aging and the effect on age-related diseases.

7.1.- Supplementation with CoQ_{10} improves many age-related dysfunctions.

As it has been indicated in previous sections, CoQ_{10} treatment improves many dysfunctions associated with aging and age-related diseases. Dietary CoQ_{10} is highly incorporated by white blood cells, spleen, thymus, liver, adrenal, ovaries and heart but is less incorporated by muscle, kidney or brain [172]. Further, bioavailability of CoQ_{10} in humans show very high interindividual differences that

can affect the conclusions of the studies about its effect as treatment [187]. To this, I have to add that if the cause of the reduction of CoQ levels in aged mitochondria is mitochondrial dysfunction, supplementation with CoQ can only restore the activity of mitochondria that are not severely damaged but not in highly damaged mitochondria. This is a very important issue to take conclusions in studies about the effect of supplementation with dietary CoQ and mitochondrial activity in aged organisms.

Despite these cautions, supplementation with CoQ_{10} has been suggested as a therapy to delay the progression of aging or age-related damages [185] including the earlier phases of neurodegeneration [188] or cardiac aging produced by nutritional defects during development [189] or in many other cardiovascular disorders found in aged individuals [190].

One of the most important effects on aging health of CoQ_{10} supplementation is to prevent cardiovascular dysfunction. Low circulating CoQ_{10} during acute phase of coronary disease is associated with inflammation and mortality [153]. Many studies have demonstrated that supplementation with CoQ_{10} and selenium improves cardiovascular activity even in elderly people [191, 192]. Moreover, CoQ_{10} has been also associated with the prevention of fibrosis in heart [193, 194] and cardiac aging in a rat model of poor maternal nutrition [189]. Vascular senescence is a key factor in the development of atherosclerosis and in this process, inflammation and mitochondrial dysfunction plays an essential role [195]. CoQ_{10} also prevents senescence of vascular endothelial cells [137] and is considered in the treatment of endothelial dysfunction [196]. Protection against oxidative damage and mitochondrial dysfunction seems to be the key antiaging activity of CoQ_{10} in endothelial cells [72, 197].

Many other studies have demonstrated the positive effect of CoQ_{10} supplementation in the delay of aging markers in different organs and tissues [185, 186]. For example, treatment with CoQ_{10} in mitochondria isolated from diabetic Goto-Kakizaki rats, prevents mitochondrial dysfunction and ROS release induced by amyloid peptide, indicating a putative protective role of CoQ_{10} therapy in Alzheimer's disease [198]. Further, CoQ_{10} also destabilizes β-amyloid fibrils impairing the progression of the amyloid plate [199]. CoQ_{10} also modulate the expression of genes involved in the inflammatory response indicating a key role

in the prevention of inflammatory damage specially in cardiovascular disease [34] or in the response of the immune system to viral infections [19]. Age-related loss of density in bone in rats fed lifelong with a fish-oil based diet is avoided by the addition of CoQ_{10} [200]. Further, CoQ_{10} supplementation has been proposed as therapy to avoid mitochondrial dysfunction in ovarian maturation [201].

All these studies and many others indicate that supplementation with CoQ_{10} can be an important therapeutic tool in the prevention of age-related mitochondrial dysfunction and the delay of age-associated diseases. Preclinical and clinical studies must be performed but taken into consideration the variability in the dietary bioavailability of CoQ_{10} among individuals and specially in aged individuals.

7.2 CoQ-derived mitochondrial-targeted antioxidants.

The low absorption of CoQ_{10} from diet and the low incorporation in some tissues and organs obligate to the use of CoQ-derived compounds such as MitoQ or idebenone [202]. These compounds are considered safe and well tolerated promising CoQ_{10} analogues able to supply CoQ_{10} deficiency in those organs that show low capacity to incorporate exogenous CoQ_{10} through blood plasma [203]. They prevent oxidative damage in mitochondrial membranes and impair the progression of mitochondrial dysfunction [204]. In fact, the use of MitoQ has been proposed in the treatment of diseases originated by the impairment of mitochondrial complex I and mDNA damage as happens in aging [205]. In cases of pathologies associated with compromised endogenous antioxidant system, treatment with MitoQ can rescue lifespan and prevent oxidative stress but not in healthy animals such as in a *Drosophila* model [206].

The CoQ_{10} derivative idebenone already showed improvement of mitochondrial oxidative metabolism in the brain of a MELAS patient, indicating the importance of antioxidant activity of idebenone in the protection of mitochondria in primary deficiency diseases [207], On the other hand, the use of MitoQ has been proposed in the treatment of neurodegenerative diseases such as Alzheimer's disease [208, 209] or in the treatment of astrocyte-associated neurodegeneration [210]. MitoQ also avoids memory loss and extends lifespan in an accelerated model of Alzheimer's disease in mice [211]. Further, treatment with MitoQ induces mitochondrial biogenesis and removal in a model of Huntington's disease

indicating the induction of mitochondrial turnover [212]. It has been recently proposed that nitrosamine stress induced by mitochondrial dysfunction in aged brain is responsible of the decrease of neurological function whereas treatment with MitoQ prevents oxidative stress and improved mitochondrial function [213].

By avoiding mitochondrial damage, MitoQ also ameliorates age-related arterial endothelial dysfunction in mice model indicating its putative use as therapeutic compound in the prevention of atherosclerosis [214]. Treatment with MitoQ also reversed in vivo aortic stiffness in old mice [215] by reducing mitochondrial reactive oxygen species [216]. Moreover, MitoQ also reverses age-related vascular dysfunction in a nitric oxide-dependent mechanism in skeletal muscle fed arteries [217]. The studies of this compound in aging must follow in order to clarify controversial results as the null effect of MitoQ mesylate in muscle aging [218].

Most of the studies with MitoQ, idebenone or other mitochondria-targeted antioxidants demonstrate that their protective effect is based on the reduction of ROS production and oxidative damage in aging [219, 220]. Maintenance of endogenous CoQ_{10} levels will produce the same effect without needing treatments with these compounds but, in the case of CoQ_{10} deficiency, their activity will help to avoid mitochondrial dysfunction specially in those tissues and organs showing deficiency to capture CoQ_{10} from plasma.

7.3. Caloric restriction (CR)

CR is the most powerful non-genetic mechanism to increase longevity in organisms [221]. Among the different effects of CR, it is clearly demonstrated that mitochondrial biogenesis and improvement of the bioenergetics efficiency in cells by modulating mitochondrial activity and turnover are some of the most important [222]. These modifications reduce ROS levels and improve antioxidant activity preventing oxidative damage in cells as central prolongevity effect of CR. However, to date only a few works have shown results about modulation of CoQ-related pathways and functions by CR or nutritional modifications.

Changes in mitochondrial activity and turnover also affect CoQ homeostasis. In one of the first studies performed, CR maintained the levels of CoQ at young levels together with a reduction of lipid peroxidation in rat mitochondria [223],

however, in this study, aging increased both CoQ_9 and CoQ_{10} in these mitochondria from rat liver [223] and also reduced the ratio $CoQ_{9/10}$ probably in response to higher oxidative stress demonstrated by the levels of hydroperoxides [224]. As CoQ_{10} content was always higher in those groups showing a more pronounced oxidative state such as aged group, authors conclude that this increase responded to higher needs of antioxidant protection against oxidative damage whereas CR returned the levels to those of the youngest [224]. In other tissues, aging was associated with a decrease of CoQ_9 in skeletal muscle mitochondria whereas CR again reversed this effect [225]. This response was also found in other organs such as rat kidney and heart in which aged mitochondria showed a decrease in CoQ_9 levels that were restored by 40% CR [226].

In another model of longevity as *C. elegans*, CR did not increase CoQ levels but it reduced them and also the expression of key enzymes for the synthesis [227]. This effect was found in adult worms although not *in larvae* indicating an age-dependent effect. The different response of model organisms introduce disturbing factors in order to understand the importance of CoQ in CR response, however, we have to keep in mind that in *C. elegans*, reduction of CoQ synthesis and protein synthome members, probably causing higher oxidative stress, have been already associated with the extension of longevity [228].

In the case of CoQ-dependent plasmamembrane redox system (PMRS) very interesting changes were found in response to CR accordingly with an increase of the protection against oxidative damage. The activity of this system responded to CR in a different way depending on the age of mice [229, 230]. In liver from rats fed under CR, $CytB_5R_3$ and NQO1 activities increased in old animals but not in young animals that showed a small decrease [230]. The same effect was found in old mice liver [229] or in brain plasma membrane in which markers of oxidative damage concomitantly were reduced by CR [231]. Changes in PMRS and modulation of CoQ levels in plasma membrane produced a higher resistance against oxidative damage in liver from CR-fed old animals whereas in young animals this effect was absent. The increase in CoQ-dependent antioxidant activities was accompanied by a higher presence of CoQ_{10} in plasma membrane whereas CoQ_9 showed a decrease in rats [230] but not in mice [229]. In both

models, these changes produced a clear modification in the ratio CoQ_9/CoQ_{10} in favor of CoQ_{10} probably indicating a more antioxidant function of the form of CoQ with longer isoprene tail. Interestingly, CoQ_{10} supplementation prevented oxidative stress in membranes and increases lifespan in rats fed with a CR diet enriched in polyunsaturated fatty acids [232], in an effect directly associated with the increase of CoQ_{10} levels in plasma membrane as we found in CR-fed animals. In these animals, NQO1 present in plasma membrane decreased while CoQ_{10} levels increased accompanied by the decrease of the activity of the Mg^{2+}-Sphingomyelinase (nSMase) indicating the protection against apoptosis induced by oxidative stress and ceramide release [37]. Dietary fat used as main component in CR diet influences the levels of CoQ in membranes of muscle after 6 months of 40% CR diet. In all the CR diets: lard, soy of fish oil, nSMase activity was reduced although levels of COQ_9 and CoQ_{10} in membranes were only influenced by fish oil and not by the other fats [233]. However, these changes were found in mature animals and probably in older animals, the result can be different. In another model of CR, every-other day feeding, increased CoQ levels and activated CoQ-dependent antioxidant activities in a response that prevented oxidative damage in aged muscle [234].

The studies of CoQ levels in plasma membrane indicate that CR induces an enrichment in CoQ_{10} in rodents accompanied by higher antioxidant enzymatic activity. Coenzyme distribution in human cells depends on the secretory pathway and the endomembrane system [108]. Incubation with C^{14}-marked para-hydroxybenzoic acid, the precursor of CoQ head, demonstrate that new synthesized CoQ is rapidly found in mitochondria and mitochondrial associated membranes (MAMs) and later in endoplasmic reticulum and plasma membrane [108]. On the other hand, supplemented CoQ is able to reach mitochondria in a pathway dependent on the integrity of ER, indicating a flux between both organelles. Then, CR seems to induce a net flux of CoQ from mitochondria to plasma membrane affecting more CoQ_{10} than CoQ_9 in rodents in a balanced response to improve antioxidant protection. The mechanisms involved in these changes are yet unknown but likely, the maintenance of the ER-mitochondria connection is involved.

Some studies have addressed the question if the ratio $CoQ_{9}/_{10}$ in rodents organisms carry any physiological significance in longevity. Studies performed in cardiac mitochondria from different mammalian species indicate that as lower the amount of CoQ_{9} and higher amount of CoQ_{10}, greater longevity, indicating that changes in the ratio $CoQ_{9}/_{10}$ in mitochondria affect lifespan [235, 236]. Interestingly, these studies determined that CoQ_{9} content in cardiac mitochondria correlated directly whereas CoQ_{10} correlated inversely with the rate of superoxide generation indicating a main protective role of CoQ_{10} against oxidative damage in mitochondria [235, 236]. In agreement with this, the rate of superoxide production in submitochondrial particles of CR-fed aged animals decreased at the same time that increased antioxidant activities [237] in an effect that also can be associated with the increase of CoQ_{10} in these mitochondria [234].

In rodents, $CoQ_{9}/_{10}$ ratio varies among tissues and organs. Liver and muscle shows the highest $CoQ_{9}/_{10}$ ratio and interindividual variability whereas heart, kidney and brain exhibit the lowest ratio and variability [238]. Only one month of CR was able to induce the levels of CoQ_{9} and $_{10}$ in mice muscle at the same time that induced the decrease in mCOQ7 in agreement with the previous indicated role of this protein in longevity [239]. Further, CR also modified the $CoQ_{9}/_{10}$ ratio depending on the organ, increasing it in kidney but decreasing it in heart [238].

This decrease in the ratio probably was a response to a higher oxidative stress since vitamin E deficient animals also showed this profile. Despite the increase in total CoQ levels, old animals showed a decrease in the activity of ETC complexes that depended on CoQ and this reduction was reverted by CR indicating that the balance of CoQ and ETC activities was more adjusted in CR fed animals. Are these modifications in the $CoQ_{9}/_{10}$ ratio related with the capacity to maintain low superoxide producing structures such as supercomplexes? Interestingly, the amount of protein-bound CoQ in mitochondrial inner membrane micelles is inversely related to the rate of superoxide production [236] and probably influences the amount of supercomplexes. In fact, it has been found that CR can increase supercomplexes assembly in mitochondria [240, 241]. The role of CoQ homeostasis in the maintenance of supercomplexes in aged tissues remains to be determined.

7.4. Physical activity and exercise

Physical activity and exercise are considered prolongevity effectors that improve many metabolic activities during aging. In sedentary aged individuals, production of lipid hydroperoxides are elevated both at rest and during exercise in comparison with young individuals indicating a deficiency in antioxidant protection [242]. Exercise can induce adaptive changes in CoQ content in muscle in response to a higher need of mitochondrial activity in aerobic rich fibers muscle [243], however, this increase can be accompanied by a decrease in α-tocopherol and, then, in a decrease in the protection against oxidative damage. Endurance exercise increases mitochondrial biogenesis and CoQ_9 levels in mitochondrial muscle. This effect is accompanied by higher OXPHOS efficiency and higher ROS production at state 4 but less production at state 3 probably in response to the higher amount of mitochondria [244].

In mitochondrial encephalomyopathy, patients showing deficiencies in complex I and IV, treatment with CoQ_{10} improved mitochondrial function and a better aerobic performance during exercise indicating the importance of CoQ_{10} for a right mitochondrial activity [245]. Interestingly, the combination of ubiquinol and exercise improved the activity of skeletal muscle preserving mitochondrial structure in the SAMP8 mice model of accelerated senescence [246].

Exercise induces metabolic stress in a hormetic response that affects many physiological changes that are associated with higher longevity. As in the case of CR, aerobic exercise restores the arterial aging associated with reduced resilience and mitochondrial dysfunction [247] and exercise also induced different response of CoQ levels and activity of CoQ-dependent antioxidants depending on the age of the animals [134]. In agreement with these effects, in young rats, exercise produced a decrease in CoQ and vitamin E in plasma but, at the same time, in liver and skeletal muscle mitochondria the levels of CoQ were higher than in sedentary animals [248]. The effect of exercise on CoQ levels was organ and tissue dependent [249, 250]. In general, chronic exercise induces increases in total CoQ in many tissues and organs in rats such as in heart and slow muscle and a tendency to increase in brain, liver, kidney and fast muscle [251]. Interestingly, this effect was just the contrary in animals that practice acute exercise indicating an adaptive process in chronic exercise and the waste of CoQ due to high oxidative stress in acute exercise [251]. The effect of exercise on

CoQ-dependent antioxidant enzymatic activities is limited although the combination of exercise with resveratrol, a nutraceutical with CR-mimetic activities [252], increase the activity of $CytB_5R_3$ and its levels in mice muscle [253]. In this case, NQO1 did not show increase neither in activity nor in levels.

In human blood plasma, physical activity increases plasma CoQ_{10} and decreases lipid peroxidation in older people whereas the effect was just the opposite in young individuals [254]. On the other hand, sedentary and overweight people showed lower CoQ_{10} in plasma accompanied by higher levels of lipid peroxidation in plasma increasing cardiovascular risk [255]. All these effects indicate that physical activity and exercise can regulate CoQ levels in many organs. This effect cannot only be explained by the increase in mitochondrial levels since CoQ_{10} levels in plasma also increase in exercised old people. Probably, muscle signals from exercise can influence liver activity and increase CoQ packing into lipoproteins in liver that are released to plasma protecting lipoproteins against oxidative stress whereas in sedentary and patients suffering metabolic syndrome this mechanism is impaired [256].

7.5. Dietary interventions and nutraceuticals .

Balanced nutrition affect lifespan and longevity. Interestingly fat composition can affect mitochondrial activity, dynamics and turnover. The levels of CoQ can be affected by fat composition in diet. The unsaturation degree of dietary fat leads to different CoQ_9 and CoQ_{10} mitochondrial contents [257]. Polyunsaturated fat diet produces a significant decrease in CoQ_9 in mitochondria of rats whereas monounsaturated fat slightly increases its levels [258].

The use of many dietary bioactive compounds has been proposed to ameliorate and even prevent disease, many of them against age-related diseases [259]. Screening of compounds with prolongevity effects and their activity as mitochondrial activators and antioxidant protection increasing CoQ_{10} levels may help to maintain a balanced mitochondrial activity and CoQ levels during aging [260].

Recently, resveratrol (RSV) and coumarate have been proposed a putative donors of the aromatic ring for CoQ synthesis in mouse and human cells [261]. This could be interesting in the case of deficiency in the production of p-

hydroxybenzoic acid, the natural aromatic ring precursor for CoQ synthesis, although the low bioavailability of RSV [262] makes this compound an unlikely precursor in physiological conditions. In our hands, RSV induces higher levels of CoQ in cultured cells, however, this effect can be ascribed to the increase of mitochondrial mass instead of higher CoQ per mitochondria. Another polyphenol, Kaempferol, a flavonol found in green tea, broccoli, Brussels sprouts and many other vegetables, induces a great increase of CoQ in mouse kidney proximal tubule epithelial and in human embryonic kidney cells [263] in a process associate with its use as source of the phenolic ring for CoQ synthesis [264]. The in vivo effect of this compound would help to increase CoQ in kidney, an important organ severely affected by CoQ deficiency [265].

Regarding CoQ-dependent antioxidant activity, RSV increased protein levels of $CytB_5R_3$ in brain, kidney and liver and the protein levels of NQO1 only in muscle reducing them in liver of aged mice [250]. However, activity of $CytB_5R_3$ was not affected but in the case of NQO1, RSV increased its activity in brain, heart and liver [250]. Interestingly, RSV was able to revert the inhibitory effect of high-fat diet (HFD) in the levels of many of the mRNA transcripts for CoQ-synthome in liver, only COQ3, COQ7 and COQ10 where not affected by the treatment of HFD-fed animals with RSV [123] indicating a regulatory effect on the expression or maintenance of mRNA codifying for the proteins involved in CoQ synthesis. RSV effect on aged organisms remains to be determined and needs further research.

7.6. Pharmacological compounds

The finding of compounds able to reestablish the endogenous synthesis of CoQ_{10} would be an interesting therapeutic approximation due to the low uptake of nutritional CoQ_{10} in some organs, however, the induction of CoQ synthesis through peroxisomal inducers was absent in aged animals [266] probably indicating external factors to the CoQ-synthome that block CoQ synthesis.

Rapamycin is a promising factor in aging resembling many CR effects [267]. Rapamycin delays neurological symptoms, reduces neuroinflammation and prevents brain lesions [268]. Rapamycin has been also associated with the regulation of CoQ homeostasis since it has been associated with the response to mitochondrial stress [221]. Inhibition of mammalian target of rapamycin complex 1 (mTORC1) with rapamycin slows the progression of mitochondrial myopathy in

muscle by improving different hallmarks of mitochondrial dysfunction and by reducing the expression of activating transcription factor 4 (Atf4), mitochondrial chaperones and other markers of changes in mitochondrial bioenergetics associated with mitochondrial dysfunction [269]. Despite the general effect of rapamycin on mitochondrial diseases, experiments performed in COQ9 mutants have shown null effect of rapamycin, indicating that this compound probably needs some changes in CoQ synthesis to exerts its protective effect [270].

The biguanide metformin is widely used for treating type II diabetes and is another pharmacological compound with interesting effects in aged individuals [271]. The mechanism of action of metformin is not clear, in some studies it accumulates in mitochondria and inhibits complex I and the reduction of ubiquinone stimulating ROS production [272]. On the other hand, it has been shown that metformin inhibits the production of ROS from complex I in macrophages reducing the release of inflammatory cytokines [273]. The combination of metformin with CoQ_{10} improves mitochondrial function in a mouse model of rheumatoid arthritis through promoting mitochondrial activity [274]. As in the case of rapamycin, metformin also activates the AMP-activated protein kinase (AMPK)/mTORC1 signaling pathway. The activation of this pathway will eliminate damaged mitochondria and increase mitochondrial turnover. For this reason, metformin reverses dopaminergic neuronal death associated with the deficiency in the synthesis or CoQ in CLK-1 mutants [275].

Natural ubiquinone derivatives such as antroquinonol have been recently proposed as inducers of mitochondrial activity through activating autophagy [276, 277]. Another ubiquinone form, 4-acetylantrocamol LT3, extracted from the fungus *Antrodia cinnamomea* also inhibits mTOR and activates AMPK and autophagy [278]. Other promising compound is N-acetyl cysteine that improves mitochondrial activity and enhances $CoQ_{9}/_{10}$ levels in mice cardiomyocytes [279].

All these compounds show their prolongevity effect by inducing autophagy and mitochondrial turnover. Probably, this activation will produce the induction of CoQ synthesis to restore levels in new mitochondria and activity of complexes. However, the role of AMPK activation in CoQ induction and maintenance of CoQ homeostasis needs to be studied.

A resume of the main findings in non-genetic inteventions related with the regulation of the CoQ synthesis and homeostasis is shown in Table 1.

8. Conclusions

The importance of the decrease of CoQ_{10} during aging is considered the most clear secondary deficiency in this essential molecule. The most important problem is to determine if CoQ_{10} secondary deficiency associated with aging is a driving phenomenon or is a consequence of the accumulation of dysfunctional mitochondria. In any case, many studies have demonstrated that supplementation with CoQ_{10} improves different cell functions in aged animals by improving mitochondrial activity and also antioxidant capacity. If CoQ_{10} deficiency is part of the cause of mitochondrial dysfunction, supplementation will restore some of the mitochondrial activity indicating that CoQ_{10} deficiency can accelerate metabolic dysfunction associated with aging and age-related diseases. However, if CoQ_{10} decline is a consequence of mitochondrial dysfunction, induction of endogenous synthesis, by activation of the CoQ-synthome, will be unable to produce enough improvement in mitochondrial activity during aging. Probably, the balance between mitochondrial dysfunction and CoQ synthesis depends on the type of cells and its relationship must be clarified organ by organ.

Information about the effect of mitochondrial nutrients and pharmacological compounds that improve mitochondrial activity on CoQ synthesis and levels is needed. The maintenance of the homeostasis of CoQ_{10} levels is essential for mitochondrial health and antioxidant protection during aging. Compounds or strategies able to increase CoQ_{10} levels in organs and tissues during aging are important therapeutic agents to increase healthspan (Figure 3).

In humans, most of the studies are performed in blood plasma. The main problem resides in that CoQ_{10} levels in plasma may not reflect the right conditions of CoQ_{10} in organs and tissues. I consider that the levels of CoQ_{10} in plasma respond more to a diet condition than to the real CoQ_{10} levels in organs as important as muscle, nervous tissue, cardiovascular or immune systems. Improvements of physiology of these organs after CoQ_{10} supplementation indicate that, at least, maintenance of CoQ_{10} levels in these organs will help to maintain activity during aging. Clarification of the relationship between prolongevity effectors, mitochondrial

dynamics and turnover and homeostasis of CoQ_{10} will help in the design of strategies to improve quality of life, independence and health during aging.

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Declaration of competing interest.

The authors declare that they have no competing interests.

List of abbreviations.

ADCK: aarF domain containing kinase.

AIFM2: apoptosis-inducing factor mitochondria-associated 2 (also known as FSP1).

AMPK: AMP-activated protein kinase.

Atf4: activating transcription factor 4.

Clk-1: timing protein clk-1 homolog.

CoQ: Coenzyme Q (ubiquinone for oxidative form and ubiquinol for reduced form)

CoQ_{10}: Coenzyme Q10.

CR: caloric restriction.

$CytB_5R_3$: cytochrome B_5 reductase 3

ER: endoplasmic reticulum.

FSP1: ferroptosis suppressor protein 1.

GPx: glutathione peroxidase.

HFD: high-fat diet.

HIF-α: hypoxic inducible factor-α.

HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.

HuR: Hu antigen R; also **ELAV**: embryonic lethal abnormal vision like 1

LDL: Low-density lipoprotein.

MAMs: mitochondrial associated membranes.

mETC: mitochondrial electron transport chain.

MFN2: mitofusin 2.

MitoNEET: CDGSH iron sulfur domain 1 (CSD1)/ mitochondrial NEET protein.

MitoQ: mitochondrial targeted antioxidant Q.

mtDNA: mitochondrial DNA.

mTORC1: mammalian target of rapamycin complex 1.

mUPR: mitochondrial unfolded protein response.

NQO1: NAD(P)H quinone dehydrogenase 1

nSMase: neutral Mg2+-sphyngomyelinase.

OXPHOS: oxidative phosphorylation.

PARL: presenilin associated rhomboid like.

PDSS2: prenyl-diphosphate synthase subunit 2

PMRS: plasma membrane redox system.

Puf3p: pumilio homology domain family member 3.

ROS: reactive oxygen species.

RSV: resveratrol.

SAMP1: senescence-accelerated mouse prone 1.

SOD: superoxide dismutase.

TNF-α: tumor necrosis factor-α.

VLDL: very low-density lipoprotein.

FIGURE LEGENDS

Figure 1. Influence of CoQ_{10} levels in mitochondria and ROS. Mitochondrial levels of CoQ_{10} are high in healthy mitochondria accompanied by low release of ROS and reduced oxidative damage. Decrease in CoQ_{10} levels decrease during aging and can be responsible of the increase in oxidative damage until reaching very low levels unable to reduce oxidative damage and associated with mitochondrial dysfunction found in aging and age-related diseases.

Figure 2. Antioxidant activities of membrane CoQ. Apart of its role in mitochondria, CoQ also plays an essential role in the protection of lipids against oxidative damage inhibiting ROS production, apoptosis and ferroptosis or oxidation of blood plasma lipoproteins and reduction of cardiovascular disease risk. The activity of the enzymes that reduce ubiquinone to ubiquinol are also involved in the modulation of ROS-dependent signalling, sirtuins and bioenergetics mediators.

Figure 3. Levels of CoQ10 can be essential in the maintenance of healthy mitochondria and healthspan during aging. Direct supplementation with CoQ_{10} or treatment with antioxidant analogues or prolongetivy effectors can increase CoQ_{10} levels in mitochondria and cell membranes improving their activity and preventing oxidative damage. On the contrary, decrease of CoQ_{10} levels in mitochondria are associated with most of the age-related diseases that reduce longevity and quality of life.

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