The current coenzyme Q science and knowledge

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Abstract. *Coenzyme Q (CoQ) is a redox lipid essential for aerobic respiration and antioxidant protection. It is synthesized in each cell by a multiprotein complex inside mitochondria and incorporated in all cellular membranes. It is however an amazing molecule whose homeostasis not only depends on the proper function of biosynthesis complex but also on age, diet and the wholeness of mitochondria functions.*

Keywords: Coenzyme Q, ubiquinone, mitochondria, mitochondrial diseases

1. CoQ function.

Since the discovery of CoQ (ubiquinone) as the essential redox quinone component of the respiratory chain in beef heart (Crane et al. 1957), knowledge of properties and functions of CoQ, and its role in aging and disease has highly evolved. CoQ is present in all cells in which acts as an essential electron carrier in the respiratory chain, transporting electrons from either complex I or complex II to complex III, but also reducing complex III from other redox enzymes (Alcazar-Fabra et al. 2016). The efficiency of electron chain is due to the integration of respiratory complexes including CoQ into supercomplexes that dynamically organize the electron flux to optimize the use of available substrates (Lapiente-Brun et al. 2013). This efficiency depends strictly on the ratio of reduced to oxidized forms of CoQ (Guaras et al. 2016). It is still unknown the mechanisms that provide the appropriate amount levels of CoQ to the supercomplex structure and if total or partial contents of this carrier are integrated into the supercomplex or a free pool exists.

2 - CoQ synthesis

CoQ is synthesized by a multiprotein complex (synthome) inside mitochondria (Stefely and Pagliarini 2017) with a high level of regulation (Gonzalez-Mariscal et al. 2018). Synthome is a complex pathway which use the initial substrate polyprenyl-4-hydroxybenzoate (pp-4-HB), which is produced by the attachment of polyprenyl-PP, produced in the mevalonate pathway, to the precursor 4-hydroxybenzoate (4-HB), produced from tyrosine, by the p-hydroxybenzoate polyprenyl transferase encoded by *COQ2* gene (Desbats et al. 2016). This synthome modifies the benzoquinone ring until CoQ is produced although different reactions are still unknown as decarboxylation and hydroxylation of pp-4-HB (Acosta Lopez et al. 2019).

The CoQ biosynthesis pathway is regulated at the transcriptional level through, e.g. NF- κ B activated by mitochondrial stress (Brea-Calvo et al. 2009), at translational level by COQ7 mRNA binding to proteins (Cascajo et al. 2016), and at the post-translational levels through phosphorylation cycles of COQ encoded proteins involving PPTC7 phosphatase (Gonzalez-

Mariscal et al. 2018; Niemi et al. 2019). There are accumulated evidence that synthome would be mainly associated to the endoplasmic reticulum (ER)-mitochondria contacts domains (Subramanian et al. 2019). In this sense, mutations of genes that encode proteins located in ER-mitochondria contact sites, which are related to lipids transport into mitochondria can cause defects in CoQ biosynthesis. Mfn2 and Adck2 colocalise in the mitochondrial-associated membranes and have been demonstrated to contribute to the maintenance of the mitochondrial CoQ (Mourier et al. 2015; Vazquez-Fonseca et al. 2019).

3. CoQ and longevity

Since the discovery of clk-1/COQ7 function in regulating *C. elegans* and mouse longevity through CoQ biosynthesis regulation (Wang and Hekimi 2016), there are recent evidence that CoQ would extend longevity through endogenous stress signaling and protein synthesis downregulation (Molenaars et al. 2018; Scialo et al. 2016). It has been proposed that CoQ levels in tissues and organs are depleted during aging and depend on dietary interventions (Parrado-Fernandez et al. 2011). For example, classical studies showed that calorie restriction increased CoQ content in plasma membrane providing antioxidant protection and modulating cytosolic NAD⁺ levels in different tissues and cells (De Cabo et al. 2004; Hyun et al. 2006; Lopez-Lluch et al. 2005), recently supported because the overexpression of extramitochondrial CoQ-dependent enzymes, CYTB5R3 and NQO1, increases health- and life-span in mice (Diaz-Ruiz et al. 2018; Martin-Montalvo et al. 2016). This plasma membrane antioxidant system, in which CYB5R3 and NQO1 reduce CoQ, was demonstrated to protect cells from phospholipid peroxidation and ceramide-dependent apoptosis (Villalba and Navas 2000). It has been recently described additional components of the plasma membrane antioxidant system, which acts through ferroptosis suppressor protein1 (FSP1) reduction of CoQ (Bersuker et al. 2019; Doll et al. 2019) preventing phospholipid peroxidation and ferroptosis.

4. Essential role of CoQ in physiology

The main functions of CoQ as electron carrier in respiratory chain and as antioxidant have been studied as regulator of mitochondrial dysfunction in aging and directly involved in glucose homeostasis by regulating insulin sensitivity (Fazakerley et al. 2018). Also, supplementation of CoQ has been also successfully used to improve senescence-accelerated mice aerobic metabolism (Tian et al. 2014), and female mice fertility by improving mitochondrial efficiency (Ben-Meir et al. 2015). Interestingly, clinical trials of CoQ supplementation showed an increase in IGF-1 and postprandial IGFBP-1 levels in elderly (Alehagen et al. 2017), and plasma levels of CoQ positively correlated with the insulin level, homeostatic model assessment-insulin resistance, and quantitative insulin sensitivity check index in diabetic patients (Fallah et al. 2018; Gholnari et al. 2018; Yen et al. 2018). Also, CoQ supplementation showed the improvement of chronic inflammation by decreasing inflammatory markers as TNF- α and IL-6 (Farsi et al. 2019; Zhai et al. 2017). In fact, cardiovascular diseases are potentiated by age and is one important major cause of death in western countries, which show improvement under calorie restriction as indicated in the review by de Cabo and Mattson (de Cabo and Mattson 2019).

Mitochondrial diseases are genetic heterogeneous and tissue-specific disorders that show different severities and time-onset forms of age-associated diseases as sarcopenia and neurodegeneration (Frazier et al. 2019). A group of these mitochondrial diseases are included in the CoQ deficiency syndrome caused by a significant low level of CoQ, which is developed by mutations in COQ genes that encode for the synthome proteins, named primary CoQ deficiency (Salviati et al. 2017). However, mostly of the diseases included in this syndrome are considered secondary deficiencies because the low level of CoQ is induced as an adaptation to either electron chain defects or defective mitochondrial functions (Yubero et al. 2016). These secondary defects can cause human deterioration of muscle with weakness and exercise intolerance that finally can cause rhabdomyolysis (Jou et al. 2019), severe necropsy of neurons associated to mutations in the mitochondrial PARL protease with complex III defect (Spinazzi et al. 2019), or multiorgan

affectation caused with autosomal recessive TANGO2 mutations (Mingirulli et al. 2019). However, although it has been demonstrated that mouse models with defects in nuclear encoded factors that regulate mitochondrial DNA functions developed secondary CoQ deficiency (Kuhl et al. 2017), there is not described any mechanism to demonstrate these adaptations.

The current knowledge of CoQ functions and biosynthesis have highly evolved since its discovery in 1957 (Crane et al. 1957) demonstrating its essential function in respiration and its important nuclear function as antioxidant. CoQ homeostasis is involved in essential bioenergetics pathway, plasma membrane mediated cellular redox homeostasis and age-dependent disorders but still unknown the complete biosynthesis pathway and how CoQ levels adaptate to different pathological conditions to guarantee cell survival

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