Editorial: "Mitochondrial Coenzyme Q Homeostasis: signalling, respiratory chain stability and diseases."

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This special issue reviews the role coenzyme Q (CoQ) plays in physiological and pathological processes. CoQ is an essential component of cellular lipid membranes and has a central role in the redox reactions occurring at them. CoQ possesses a benzoquinone ring and an isoprenoid side chain with a variable number of units. The number of units differs in different species, e.g. the most common form in humans contains ten units, while it contains only six in yeast. CoQ is instrumental for electron transport both in the cell and mitochondrial membranes. Electron transport occurs through changes in the redox state of CoQ that is found oxidized (ubiquinol), semi-oxidized (semiubiquinone) or reduced (ubiquinol).

There has been increasing interest in understanding the various functions of CoQ *in vivo*, including its role as an electron carrier and antioxidant. Furthermore, due to its importance, alterations in CoQ levels or its redox state contribute to ageing and age-related diseases, and a group of mitochondrial diseases included in the CoQ deficiency syndrome. CoQ synthesis is a complex process that involves several steps occurring in different cellular compartments, including the mitochondrion. Villalba and Navas reviewed what is known and unknown about CoQ biosynthesis, discussing the different regulations that co-exist at the transcriptional, translational and post-translational levels [1]. The authors explain how the epigenome influences CoQ levels and how CoQ is responsible for epigenetic responses occurring during and after development. CoQ plays essential roles within mitochondria but also outside of mitochondria. Hernansanz and Enriquez [2] discuss the role of CoQ in the organization of the respiratory complexes in macrostructures called super-complexes. The authors describe the existence of specialized pools of CoQ, and cytochrome c, that allow optimal use of available fuel to feed the electron transport chain, reducing oxidative damage. In addition to its role in the respiratory electron transport chain, CoQ executes other essential functions inside and outside of mitochondria. Baschiera and col. [3] review these functions, discussing the consequences of CoQ depletion beyond its role as an electron carrier. For example, they examine

its role as a powerful antioxidant and how it can maintain cell survival or trigger cell death via apoptosis or ferroptosis in response to external stimuli.

Due to the importance of CoQ, it is unsurprising that alterations in its levels or redox state cause severe disease. Unfortunately, and due to the complexity of CoQ regulation and the many functions that it carries out within the cell, the diseases associated with CoQ alterations do not currently have a cure. This underlines the need to further understand and treat CoQ diseases. Three different articles review the role of CoQ in pathology. Alcazar-Fabra and col. [4] address the problem of primary CoQ deficiencies, outlining the many mutations found in patients and the symptomatology associated with them. They describe how the lack of a clear correlation between phenotype and genotype complicates and hinder the diagnosis and treatment of CoQ deficiency syndrome. Their article provides clinicians with an online tool to help in the diagnosis of CoQ primary diseases. Gueguen and col [5] discuss the importance of secondary coenzyme Q deficiencies. These alterations are characterized by CoQ depletion in the nervous or muscular systems that is not caused by mutations in CoQ synthesis machinery. The fact that CoQ depletion is common to many different diseases has driven work related to the identification of pathways to restore CoQ levels. Theoretically, supplementation of CoQ can restore normal concentrations in deficient cells. However, the reality is that supplementation is very challenging due to low bioavailability of CoQ supplements. Since CoQ administration has been trialled for many genetic and non-genetic diseases with mixed results, further research is warranted. An excellent example of the former is heart failure. Heart failure is one of the leading causes of death worldwide. Yuan and col [6] review how CoQ intervenes in heart failure, discussing the available data supporting a role for CoQ dysfunction and the clinical trials studying the effects of CoQ supplementation.

Finally, we have three articles addressing the role of CoQ in ageing. Ageing is one of the most critical issues the world will confront during this century. The leading role of CoQ in electron transport and as an antioxidant makes it unsurprising that CoQ frequently appears in ageing research. Lopez-Lluch [7] analyses how CoQ levels and redox state changes contribute to ageing and the onset of age-related diseases. Thus, he brings together the various interventions tested to reverse age-related alterations in CoQ levels and discusses how they impact longevity and healthspan. Scialo and Sanz [8] revise how the redox state of CoQ regulates the production of mtROS by the electron transport chain and how CoQ-ROS signalling is essential for maintenance of redox signalling and stress adaptation. They describe how mtROS production changes during ageing and how the former impacts redox signalling and triggers oxidative damage. Marcheggiani and col [9] present a new model to study cellular senescence based on depletion of CoQ using statins. Since CoQ levels could be restored by supplementation, their model allows the study of the role of mitochondrial dysfunction in cellular

senescence and the generation of the senescence associated secretory phenotype that causes inflammation and can contribute to the onset of cancer and other diseases.

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