Chapter 5

Regulation of Synthesis of Coenzyme Q₁₀

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Abstract The regulation of gene expression needs many mechanisms of control which are multiple and diverse, encompassing from DNA structure to synthesis, modification and location of proteins. These processes, in addition to being tissue-specific, change during embryonic development and throughout the life of the organism. CoQ₁₀ is essential to maintain cell homeostasis and to increase life-span. CoQ₁₀ biosynthesis pathway is strictly regulated and this program involves different levels of regulation (transcriptional, post-transcriptional and post-translational). Here we have focused on processes of post-transcriptional regulation governed by RNA-binding proteins (RBPs) and review the role of these RBPs in senescence and aging. Finally, we report post-transcriptional and post-translational events involved in the regulation of several *COQs* genes involved in the CoQ₁₀ synthesis complex assembly. The knowledge of processes that control CoQ₁₀ levels in cells is key to develop therapies to stimulate the endogenous synthesis of CoQ₁₀.

Keywords Coenzyme Q · Protein stability · Protein regulation · HuR · RNA binding proteins (RBPs)

5.1 Introduction

The expression of genes changes enormously along the life of organisms. The set of genes characterizing each cell and tissue in different stage of the development are transcriptionally regulated by different transcription factors that bind to regulatory elements located normally near the promotor or each gene. However, this is not the only level of regulation that affects the transit from DNA to protein, several post-transcriptional regulatory processes are also involved in the control of the levels of the proteins codified by these genes. This post-transcriptional regulation involves

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processes related with mRNA metabolism, such as splicing, nuclear export, cytoplasm localization, stability and translation (Glisovic et al. 2008; Mata et al. 2005; Zhao et al. 2017).

Many authors defend the existence of common expression patterns occurring in a coordinated way. Thus, cells are able to adapt and respond coordinately to different alterations or stimuli. This adaptation also occurs during aging. Many of mRNA encoding proteins related with aging are associated to RNA-binding proteins (RBPs) which regulate protein production, at least in part, by modification of the mRNA stability and translation level (Masuda et al. 2012). These post-transcriptional regulation processes involve cis-acting elements in the RNA molecule, such as AU-rich elements (AREs) generally located at the 5' and 3'mRNA untranslated regions (UTR), and polyA tail. AREs play a critical role in the regulation of gene expression during cell growth, differentiation, immune response and cancer (Chen and Shyu 1995).

AREs are responsible for regulating the stability of transcripts (Franks and Lykke-Andersen 2008; Pesole et al. 2001). The regulation of these elements is important during aging since many senescence-associated genes contain ARE sequences (Borbolis and Syntichaki 2015). These motifs specifically interact with trans-acting factors, microRNA and RNA-binding proteins, forming ribonucleoprotein complexes (RNPs) (Krecic and Swanson 1999). These interactions are very dynamic and RNPs composition depends on cell type, growth conditions, cell compartment and target mRNA (Masuda et al. 2009). In this chapter, we will focus in RBPs and its function in cellular senescence, aging and control of the members of the CoQ synthesis complex.

5.2 Molecular Mechanisms of mRNA Stability Regulation

The molecular mechanisms by which RBPs regulate mRNA stability are still not completely clarified. Among RBPs, several of them, decrease the mRNA stability whereas others stabilize mRNA and even regulate translational rate. RBPs associate mRNA with cellular structures such as exosome, processing P-bodies and stress granules involved in the mRNA turnover (Adjibade and Mazroui 2014; Chen et al. 2001; Kedersha and Anderson 2002; Sheth and Parker 2003; von Roretz et al. 2011). Some RBPs increase half-life of mRNA through a binding competition preventing the association of destabilizing RBPs (Kuwano et al. 2008). It has been also described that several RBPs act at the translational level, specifically during initiation, elongation and/or termination regulating the translation rate of transcripts with which they interact (Kawai et al. 2006; Mazan-Mamczarz et al. 2006).

Different RBPs include some proteins that show affinity for the same mRNA. Consequently, these proteins probably associate and function in a cooperative or competitive manner on the regulation of the same target mRNA (Lal et al. 2004). Among the RBPs identified involved in senescence and aging, we can find stabilizing proteins such as HuR, a RBP ubiquitously expressed belonging to ELAV

(embryonic lethal abnormal visual)/Hu protein family (Herman and Autieri 2017) and QKI, Quaking RBP (Darbelli and Richard 2016). AUF1, ARE /poly(U)-binding/degradation factor 1 (Gratacos and Brewer 2010), CUGBP1, a member of the CUG-BP- and ETR-3-like factors family (Jones et al. 2012), KSRP, KH-type splicing regulatory protein are involved in alternative splicing, destabilization and translation enhancement (Apponi et al. 2011). CRT, calreticulin (Timchenko et al. 2002), and TTP, tristetraprolin (Apponi et al. 2011) regulate the destabilization of mRNA. On the other hand, other RBPs show dual activity, for example TIA-1, T-cell restricted intracellular antigen 1, that functions as a translational repressor of mitochondrial proteins such as cytochrome c (Kawai et al. 2006) whereas promotes mitochondrial fragmentation by enhancing mitochondrial fission factor translation (Tak et al. 2017). In general, all these proteins have been associated with the regulation of transcripts and translation during development and aging (Campos-Melo et al. 2014; Kai 2016; Kim et al. 2017). Among the proteins regulated by the RBPs, we can find the cyclin kinase inhibitors p16, p21 and p27 and cyclins A and B (Cho et al. 2010; Kullmann et al. 2002; Wang et al. 2000, 2005). Levels of these proteins change with age, and they are involved in stress response, proliferation and cell cycle control.

5.3 RBPs-Dependent Regulation of mRNA Stability in Cell Growth and Senescence

Cellular senescence is the process by which cells remain retained in cell cycle, after a finite number of divisions, but they are viable and metabolically active for a long time. HuR is one of the most studied RBP and has been associated with cell senescence. This family also includes HuB, HuC and HuD, which are expressed predominantly in neurons. HuR has three RNA-recognition motives (RRM) through which it binds to AU and U-rich elements mainly located in 3'UTR of the transcripts (Lopez de Silanes et al. 2004; Ma et al. 1996; Peng et al. 1998). Although, HuR is found primarily in the nucleus, its function on target mRNA depends of its cytoplasmic localization (Atasoy et al. 1998). In fact, HuR can be shuttled between nucleus and cytoplasm through its RNS sequence (shuttling sequence) located between second and third RRM (Fan and Steitz 1998).

Cell cycle progression depends on HuR cytoplasmic level since HuR regulates mRNA encoding cyclins A and B1 (Wang et al. 2000). The stability of both cyclins increases by HuR interaction. Conversely, reduction of HuR level destabilizes the mRNA of cyclin A, B1 and c-fos mRNA, decreasing its respective protein level and thereby inducing cell senescence (Wang et al. 2000). The effect of HuR is controlled by a methyltransferase (CARM1) that enhances the regulatory capacity of HuR on these mRNAs (Pang et al. 2013). Further, it's been shown that this RBP binds to the cyclin kinase inhibitor p27^{kip1} mRNA at its 5'UTR inhibiting its translation (Kullmann et al. 2002). Since p27^{kip1} binds to cyclin E/Cdk2 or cyclin D/Cdk 2

inhibiting the progression through G₁ phase of the cell cycle, its inhibition by HuR will reduce the possibility of cell cycle blocking (Polyak et al. 1994). On the other hand, interaction of HuR to p16/INK4 3'UTR induces a decrease of mRNA stability, by recruitment of another RBP, AUF1 (Chang et al. 2010).

HuR also regulates stress and immune response proteins, such as, c-myc, vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF)-1, prothymosin, cyclooxygenase (COX)-2, tumor necrosis factor-alpha (TNF- α), and several interleukins, indicating a putative role in the control of the immune system and in immunosenescence (Casolaro et al. 2008; Dean et al. 2001; Galban et al. 2008; Lal et al. 2005; Levy et al. 1998; Liu et al. 2009; Sengupta et al. 2003).

Expression of three RBPs, HuR, AUF1 and TIA-1, were analyzed in a model of cellular aging, such as human diploid fibroblasts (HDF) in culture (Wang et al. 2001). In these cells, the interaction of RBPs to target transcripts decreased during replicative senescence, so this situation induced a reduction of mRNA stability and the level of protein regulated by HuR. On the other hand, HuR, AUF1 and TIA-1 level studied from biopsies of different human tissues and different age (fetal, young, adult and old) remains unchanged, or even a slight increase in lung and intestine, suggesting that HuR is functional during tissue aging (Kim et al. 2017; Masuda et al. 2009; Pesole et al. 2001). The reduction of HuR protein expression in senescence seems to be due to a lower translation rate, because mRNA levels remain unchanged. Additionally, HuR cellular distribution changes during senescence (Yi et al. 2010). In a positive feedback, HuR can associate to 3'UTR of HuR mRNA regulating the nuclear export and consequently increasing the HuR translation rate. This mechanism of regulation might explain the progressive loss of HuR protein during senescence and increase in cancer model.

The discrepancies between these studies raises the differences between in vivo and HDF in culture senescence. Scientific community agrees that senescence of HDF cells recapitulates some features of elderly cells although not all of them in the whole organism. Senescent cells accumulate with age and they contribute to process of aging by accelerating the tissue regeneration loss. However, the exact connection between cellular senescence and aging is still not clear. All these works show the need to deepen in study of senescence models used and the influence of RBPs in this process.

5.4 Deregulation of the Stability of mRNA Is Associated with Aging and Age Related Diseases

Aging is accompanied by multiple levels of deregulation of several systems affecting cells and tissue in different ways. In the case of mRNA stability, the role of RBPs in the decline of functionality of organs and tissues is not completely clear. However, although the information about the functions of these proteins in the response of organs such as muscle to disuse, aging or exercise, is limited, it has been

recently proposed that the dynamic changes in RBPs can play a key role in the response of muscle to muscle loss in aged people (Van Pelt et al. 2019).

Differences in the profile of transcripts during aging are clear although the mechanisms involved have not been clarified to date. In studies carried out in human cohorts, the profile of N6-methyladenosine (m6A) decreases and this decrease negatively affects the levels of several mRNAs (Min et al. 2018). Dysregulation of mRNA stability has been associated with aged tissues and importantly with the progression of age-associated diseases like atherosclerosis and inflammatory profile (Herman and Autieri 2018; Masuda et al. 2009). However, the information about the dynamic of RBPs during aging and immunosenescence is not clear and needs further research (Herman and Autieri 2018).

In the case of mitochondrial dysfunction as hallmark of aging, RBPs can be involved in a vicious cycle. The mechanism of response to mitochondrial protein stress, named mitochondrial unfolded protein response (mtUPR), is essential to maintain mitochondrial turnover (Yi et al. 2018). However, in some cases this mechanism can be blocked by mRNA instability that affects aging or the progression of aging-related diseases. The response to mtUPR seems to depend on a mitochondrial transporter known as ABCB10. Deletion of this protein causes increase of ROS levels and cell death indicating an important role in mitochondrial activity. Huntingtin, the protein involved in Huntington's disease, decreases the levels of ABCB10 protein by reducing the stability of its mRNA and decreases its translation (Fu et al. 2019).

5.5 Post-transcriptional Regulation of CoQ₁₀

Regulation of the half life of mRNA transcripts and translation rate of the components of the CoQ₁₀ synthesis machinery is not clear. We have found organ-dependent changes in the levels of the transcripts of many of these genes along mice life showing a puzzling regulation. In many of the organs, especially in those showing mitotic capacity, the mRNA levels of the components of the synthesis increase during maturity and decrease to young levels or less in the case of aged animals (Campos-Silva et al. 2017). This behavior of the COQs transcripts resembles the pattern of expression found in humans in which the levels of expression of miRNAs in centenarians are more similar to the pattern in young people than to the pattern in octogenarians (Serna et al. 2012). In fact, centenarians seem to maintain the capacity to produce microRNAs whereas this pathway is impaired in octogenarians (Borras et al. 2017) and their transcriptome is distinct from septuagenarians, probably indicating the induction of regulatory pathways involved in survival at very advanced ages resembling the regulation of young people (Borras et al. 2016).

As it has been previously indicated in Chap. 2 of this book that Coenzyme Q (CoQ₁₀ in human and CoQ₆ in yeast) is a lipid endogenously synthesized in mitochondria, and it is present in all the cell membranes. CoQ biosynthesis pathway is a complex process that involved at least the product of 13 genes in mammals (COQs

and *ADCKs*). The products of *COQs* genes form a multi-enzyme complex, anchored in the inner mitochondrial membrane. PDSS1, PDSS2, COQ2, COQ3, COQ5, COQ6 and COQ7 proteins play an enzymatic function. The role of several other proteins is still unknown, such as COQ4, COQ8A, COQ8B, COQ9, COQ10 and COQ11 and some authors hypothesized that they play regulatory functions (Stefely and Pagliarini 2017).

Homeostasis of ubiquinone is essential to maintain mitochondrial function, and therefore, to keep appropriate physiological activities in the cell. CoQ content and *COQs* gene regulation change in function of tissue, nutritional, physiological and pathological conditions and it's known that CoQ is essential in the longevity of different animal models (SPAcosta et al. 2016; Linnane et al. 2002; Navas et al. 2005; Parrado-Fernandez et al. 2011). We have found that gene expression patterns change enormously throughout the life of an organism (Campos-Silva et al. 2017). All these evidences suggest that biosynthetic pathway must be tightly regulated, including several levels of regulation (transcriptional and post-translational), to balance oxidative phosphorylation and adapting to changes in nutritional and/or physiological conditions and mitochondrial activity.

In humans, deficit of CoQ₁₀ induces heterogeneous and very severe symptoms, such as nephrotic syndrome, encephalomyopathy and ataxia (Quinzii et al. 2007). CoQ₁₀ deficiency is considered a rare disease caused by either mutation in any gene involved in its biosynthesis (primary deficiency) or by other mitochondrial dysfunctions producing CoQ₁₀ deficiency in which CoQ-synthome is not be directly affected (secondary deficiency) (Doimo et al. 2014; Kuhl et al. 2017; Yubero et al. 2016).

Regulatory mechanisms of CoQ biosynthesis include transcriptional regulation of enzymes in the mevalonate pathway, which is shared with other lipids such as dolichol and cholesterol, via the transcriptional factor PPAR α (Bentinger et al. 2008; Bentinger et al. 2003). The transcriptional induction of *COQ7* expression has been associated to the activity of NF- κ B in response to oxidative stress and probably in inflammation responses (Brea-Calvo et al. 2009). Interestingly, CoQ₁₀ has been associated with the regulation of NF-E2 related factor 2 (NRF2)/antioxidant response element (ARE) in many systems (Choi et al. 2009; Li et al. 2016), but, despite its important role as antioxidant (Chap. 3 in this book), this regulatory factor has not been directly related with the control of *COQs* gene expression.

Several findings have demonstrated that, in many cases, there is not a direct relationship between mRNA and protein levels. In these cases, increase at the mRNA levels are not accompanied by high protein amount indicating the presence of post-translational mechanisms of regulation affecting mRNA stability and/or translational rate (Lohman et al. 2014; Luna-Sanchez et al. 2015). Recent literature highlights the importance of post-transcriptional regulation of *COQ* genes and the structure of the complex of CoQ synthesis in the modulation of ubiquinone levels. At post-transcriptional level, it has been described that mRNA-binding proteins (RBPs) regulate CoQ₁₀ biosynthesis. Specifically, HuR and hnRNP C1/C2 bind to 3'UTR of COQ7 mRNA modulating the stability and translation of the transcript of COQ7. HuR and hnRNP C1/C2 play opposite roles. Whereas HuR stabilizes COQ7 mRNA, maintaining the physiological level of protein, hnRNP C1/C2 induces

Fig. 5.1 Regulation levels of CoQ₁₀ biosynthesis. Synthesis of CoQ₁₀ depends on several levels of regulation. 1. Transcriptional regulation is not completely known since many of the probable transcriptional factors involved in the expression of the members of the Q-synthome are not known yet. 2–5. Regulation of the mRNA processing, such as transport, location, stability and translation control depends on RBPs and these processes seem to be key points in regulation of the synthesis of CoQ₁₀. 6. Post-translational modifications involve putative phosphorylation points and proteolysis into mitochondria. 7. Proteins are finally assembled in a multicomplex and it is also an essential regulation point at the end of the process

COQ7 mRNA destabilization (Cascajo et al. 2016). Through these factors, the dynamic of COQ7 mRNA would depend on the specific tissue and on metabolic and stress conditions.

In the case of COQ3 and COQ6 transcripts, it seems that they could be possible targets of the Clu1/CluA homologue (CLUH) (Gao et al. 2014). CLUH binds to several mRNA of nuclear-encoded mitochondrial proteins and also induces mitochondrial clustering, probably linking the biogenesis of mitochondrial proteins with the distribution of the organelle. Although these authors did not demonstrate specifically the function of this RBP in *COQs* genes, they showed that CLUH depletion reduces the translation of several of its target proteins. Another member of the CoQ-synthome, COQ5, has been shown as a target of Puf3 in yeast (Lapointe et al. 2018). In fact, this RBP regulates CoQ6 biosynthesis in yeast (Garcia-Rodriguez et al. 2007; Lapointe et al. 2018). All these results support the idea that post-transcriptional regulation through RBPs regulating mRNA half life and translational rate is a key process in control of CoQ homeostasis (Figs. 5.1 and 5.2).

Fig. 5.2 mRNA regulatory processes of members of the Q-synthome. RBPs bind to mRNA at the 5'UTR or the 3'UTR ends. 5'UTR binding proteins regulate translation rate of the mRNA and can control the level of protein. Probably RBPs bound to the 3'UTR control mRNA stability, thus keeping the level of mRNA available for quick synthesis of proteins.

5.6 Post-translational Regulation of CoQ₁₀ Synthesis

Although it is clear that CoQ₁₀ synthesis is driven by a complex of proteins, the interactions between these proteins and the regulation of the activity of the synthome remains elusive. Post-translational modifications of COQs proteins such as phosphorylations and proteolysis also regulate the biosynthesis of CoQ. PPTC7, a human mitochondrial phosphatase, modulates CoQ₁₀ content by controlling COQ7 phosphorylation (Gonzalez-Mariscal et al. 2018; Niemi et al. 2019; Stefely et al. 2015; Xie et al. 2011). No further regulation by phosphorylation has been suggested although many of the members of the CoQ-synthome show putative phosphorylation sites.

Regarding proteolytic processes, COQ5 has been suggested to be a target of the mitoprotease Oct1p. Proteolytic modification of COQ5 improves protein stability and in consequence CoQ₆ synthesis in yeast (Veling et al. 2017). On the other hand, we have recently found that PARL, a human protease found in mitochondria, is involved in CoQ₁₀ biosynthesis and cell respiration by regulating COQ4 and UQCRCF1, a respiratory Complex III subunit (Spinazzi et al. 2019).

Other regulatory mechanisms of CoQ synthesis have been recently described. Some of the COQ proteins, with yet unknown function (COQ4, COQ9 and COQ8), would coordinate the association between CoQ precursors and enzymatic proteins to regulate the assembly of the CoQ synthesis complex (Kamzalov and Sohal 2004; Marbois et al. 2009; Zampol et al. 2010). Specifically, COQ9 protein interacts with COQ7 affecting both level and enzymatic function of COQ7 protein in mice (Lohman et al. 2014). This result is also supported by the fact that patients with *COQ9* mutations show reduced levels of COQ7 protein (Danhauser et al. 2016). These authors showed that COQ9 stabilizes other COQs proteins and they suggest that this regulatory process is tissue-specific. In addition, it has been described that COQ9 possess lipid-binding activity (Lohman et al. 2014). Both CoQ and its precursors are extremely hydrophobic due to isoprenoid tail, which keep it embedded within of mitochondrial inner membrane. This tail is attached to polar head that is sequentially modified by enzymatic COQ proteins to produce the mature CoQ

molecule. In addition to binding and stabilizing COQs proteins, COQ9 is capable of interacting with different lipid intermediates of CoQ synthesis pathway. In fact, other non-enzymatic proteins of CoQ pathway, such as COQ8/ADCK3 or ADCK4, also show lipid-binding activity (Reidenbach et al. 2018).

On the other hand, other processes not directly involved in CoQ₁₀ synthesis can influence the structure of the complex. It has been demonstrated that head-modifying enzymes are specifically organized into domains inside mitochondria, both in yeast and human cells. Concentration and distribution of these domains depend on functional status of CoQ biosynthesis pathway. ER-mitochondrial contacts are enriched sites in lipids and enzymatic proteins that could play an important role in this regulatory process (Subramanian et al. 2019). In fact, mitofusin 2 protein, a key factor in mitochondrial fusion/fission dynamics, is enriched in ER-mitochondrial contacts and is required to maintain CoQ levels in cells (Mourier et al. 2015).

According to our recent studies, ADCK2 emerges as other protein with regulatory function in CoQ synthesis (Vazquez-Fonseca et al. 2019). ADCKs (ADCK1–5) are domain-containing mitochondrial protein kinases, but their functions need to be studied in more details (Vazquez-Fonseca et al. 2019). Recently, we have found that lipid metabolism and CoQ biosynthesis are affected by ADCK2 mutations in mice and humans. In fact, it has been proposed that ADCK2 could be involved in transport of lipids inside the mitochondria. More experimental approaches are needed in order to demonstrate if ADCK2 have a role in CoQ domains and ER-mitochondrial contacts.

All these elements are required to maintain the concentration and spatial distribution of lipid intermediates, adequate protein levels for the synthesis of CoQ₁₀, and, in consequence, an efficient CoQ₁₀ homeostasis within the mitochondria and other cell membranes. All these processes of regulation, from *COQ* gene expression (transcriptional control), to mRNA metabolism, protein synthesis (post-transcriptional control) and protein complex assembly (post-translational control), might be perfectly coordinated. It seems that they can be tissue-specific and they are probably associated with mitochondrial turnover and dynamic, being for this reason modulated throughout development and life of an organism. Because alterations in any of these mechanisms could cause a CoQ deficit, their knowledge would help to develop specific therapies to modulate CoQ content.

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