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Review

Nuclear–mitochondrial interaction

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Abstract

The biogenesis of mitochondria depends on the coordinated expression of nuclear and mitochondrial genomes. Consequently, the control of mitochondrial biogenesis and function depends on extremely complex processes requiring a variety of well orchestrated regulatory mechanisms. It is clear that the interplay of transcription factors and coactivators contributes to the expression of both nuclear and mitochondrial respiratory genes. In addition, the regulation of mitochondria biogenesis depends on proteins that, interacting with messenger RNAs for mitochondrial proteins, influence their metabolism and expression. Moreover, a tight regulation of the import and final assembly of mitochondrial protein is essential to endow mitochondria with functional complexes. These studies represent the basis for understanding the mechanisms involved in the nucleus–mitochondrion communication, a cross-talk essential for the cell.

Keywords: Mitochondria; Transcriptional factors; Post-transcriptional regulation; RNA-binding proteins

1. Introduction

Eukaryotic cells contain a large number of mitochondria, which are essential for cell metabolism. In fact, these organelles perform pyruvate dehydrogenation, Kreb's cycle, and oxidative phosphorylation, the energy-generating processes coupling the oxidation of substrates to the synthesis of nearly all cellular ATP. In addition, mitochondria are involved in the synthesis of amino acids, nucleotides, and lipids, in ion homeostasis and in cell proliferation, motility and programmed death (Schatz, 1995; Ackerman and Tzagoloff, 2005; Caruso et al., 2007). Mitochondria malfunctioning is related to aging and to the onset of many diseases, including cancer (McKenzie et al., 2004; Brandon et al., 2006; Modica-Napolitano et al., 2007). The number, structure, and functions of mitochondria differ in animal cells and tissues in relation to the energetic needs (Yaffe, 1999; Nagata, 2006), and they can vary during development and differentiation, or in response to physiological or environmental alterations (Pollak and Sutton, 1980; Cuezva et al., 1997; Enriquez et al., 1999; Moraes, 2001). Mitochondrial proliferation occurs in response to electrical stimulation of muscle, following training exercise (Hood, 2001) and during thermogenesis adaptation in rodent brown fat (Klingenspor et al., 1996). Proliferation of defective mitochondria takes place in certain mitochondrial myopathies, in which affected muscles are characterized by the presence of ragged red fibres (Moraes et al., 1992). Presumably, this proliferation is a nuclear response to mitochondrial DNA (mtDNA) mutations leading to deficiencies in ATP production, but the mechanisms underlying these events are poorly understood at the molecular level. Mitochondrial proliferation and massive amplification of mtDNA take place during oogenesis in sea urchin. The resulting mitochondrial genomes are distributed to the embryo cells until very late developmental stages, when embryonic mtDNA replication resumes (Matsumoto et al., 1974; Rinaldi et al., 1979a,b). Interestingly, mitochondrial mass in *Paracentrotus lividus* embryos is constant during development, while respiratory activity is enhanced at fertilization and increases from 16 blastomeres until gastrula (Morici et al., 2007). Experiments on enucleated sea urchin eggs

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demonstrated that a negative control is exerted by the nucleus over mitochondrial mtDNA activity: mitochondrial DNA does not replicate, and it is not transcribed, as long as the nucleus is present (Rinaldi and Salcher-Cillari, 1989). Mitochondrial genome consists of a double-stranded covalently closed circular DNA molecule of about 16.5 kb in vertebrates. Many mtDNA molecules are packaged within mitochondria into small clusters called nucleoids (Jacobs et al., 2000), or chondriolites, that vary in size and number in response to physiological conditions (Nosek and Tomaska, 2003; Legros et al., 2004; Malka et al., 2006). Nucleoid structure is stabilized by TFAM, or mtTFA, which binds to mtDNA and regulates its abundance (Kanki et al., 2004). The maintenance of the integrity of mitochondrial DNA is important for keeping proper cellular functions both under physiological and pathological conditions (Kang et al., 2007). Mitochondria contains about 1500 different proteins, only half of which have been identified (Calvo et al., 2006). Metazoan mtDNA encodes 13 mRNAs for subunits of the oxidative phosphorylation complexes (OXPHOS) (Anderson et al., 1981; Taanman, 1999; Fernandez-Silva et al., 2003). Proteins of mitochondrial origin are translated on mitochondrial ribosomes bound to the matrix side of the inner membrane, and co-translationally inserted into the proper compartment (Poyton and McEwen, 1996; Allen et al., 2005). All the other mRNAs for mitochondrial proteins are transcribed in the nucleus (Saraste, 1999) and translated by cytoplasmic ribosomes. Proteins are eventually imported into mitochondria (Glick and Schatz, 1991) and distributed to different compartments (inner and outer membrane, matrix and intermembrane space) (Poyton and McEwen, 1996). These two pathways must converge at some point for those multimeric complexes assembling nuclear and mitochondrial gene products. It is noteworthy that the machineries for both pathways are composed entirely by nuclear-coded proteins. Recently, by genomic and proteomic approaches, experiments were devoted to identify new pathways for the biogenesis of the inner and outer membranes, for the assembly and export of proteins from matrix to the inner membrane and for the addition of new components to the existing pathways (Meisinger et al., 2007).

One group of nuclear genes contributes with catalytic and auxiliary proteins to the mitochondrial enzymatic activity. A second group includes all the factors that regulate the expression of nuclear and mitochondrial OXPHOS genes (Scarpulla, 2006), while a third group encodes factors responsible for the import, assembly, and final localization of mitochondrial polypeptides (Neupert, 1997; Koehler, 2004). Thus, nuclear genome has a leading role in the biosynthesis of the respiratory chain (Khalimonchuk and Rödel, 2005; Scarpulla, 2006), nevertheless, although relatively few, mitochondrion-encoded proteins participate in the formation of mitochondrial oxidative phosphorylation complexes (Attardi and Schatz, 1988; Capaldi, 1990). Moreover, nuclear activity can be modulated by signals sent by mitochondria (Liu and Butow, 2006).

2. Transcriptional regulation

The identification of transcription factors regulating the expression of nuclear genes encoding mitochondrial respiratory components represents a good experimental tool for elucidating the mechanisms involved in the intergenomic cross-talk (Garesse and Vallejo, 2001). In general, it is thought that several regulatory circuits might exist in response to different physiological stimuli, or that different regulatory pathways are activated for the expression of different groups of genes. In other words, several factors regulating the transcription of many nuclear genes for mitochondrial proteins were isolated, but so far no common feature has been identified for the regulation of all involved genes in a coordinated manner (Goffart and Wiesner, 2003; Scarpulla, 2006). The promoters of many genes coding for OXPHOS proteins and other mitochondrial enzymes were characterized. It was demonstrated that they do not exhibit canonical TATA and CAAT boxes, have heterogeneous initiation sites, and contain complex and promoter-specific regulatory regions that can differ even among genes encoding subunits of the same complex (Garesse and Vallejo, 2001). The expression of many proteins of the OXPHOS complexes, like cytochrome *c* oxidase, the terminal component of mitochondrial respiratory chain, is regulated at transcriptional level through specific nucleus-encoded factors (Lenka et al., 1998; Scarpulla, 2002a,b). NRF1 (nuclear respiratory factor 1), the first isolated mammalian factor common to the expression of nuclear respiratory genes, functions as a positive regulator of transcription (Scarpulla, 2002b; Kelly and Scarpulla, 2004). The target genes of NRFs (NRF-1 and NRF-2) encode subunits of the OXPHOS complexes or proteins involved in the expression, assembly, and function of the complexes (Scarpulla, 2006). In mammals, it has been demonstrated that NRF-1 is able to bind the promoters of genes encoding components of mtDNA transcription machinery (TFAM, TFB1M, TFB2M, and POLRMT) (Cam et al., 2004), whose mechanisms of action are being established (Asin-Cayuela and Gustafsson, 2007). Moreover, NRF-1 seems to be related to the expression of mitochondrial and cytosolic enzymes of the heme biosynthetic pathway, and to components of the protein import and assembly machinery, suggesting that it plays a role in nuclear–mitochondrial interactions (Scarpulla, 2006). NRF-2 regulates the transcription of mtTFA in human, mouse, and rat (Kelly and Scarpulla, 2004), and mtTFA is responsible for the transcription of the mitochondrial-encoded COX subunits I, II, and III, that are transcribed polycistronically (Fisher and Clayton, 1988; Larsson et al., 1998). Ongwijitwat and Wong-Riley demonstrated that, in neurons, NRF-2 is able to regulate all the nuclear-encoded COX subunits at the transcriptional level. Thus, NRF-2 may play a critical role in regulating the synthesis of the cytochrome *c* oxidase subunits in response to changes in neuronal energy demand (Ongwijitwat and Wong-Riley, 2005). Human cytochrome c_1 promoter seems

to be modulated by two transcription factors, E2F1 and E2F6, but they do not exert the same effects on other additional promoters of OXPHOS genes, suggesting that the members of the E2F family are not general modulators of OXPHOS gene expression (Luciakova et al., 2000). The activity of transcription factors is increased by coregulators, which usually exist as multiprotein complexes in the nucleus. This class of proteins can be highly regulated and represents the primary targets of hormonal control and signal transduction pathways (Spiegelman and Heinrich, 2004). The PGC-1 (peroxisome proliferator-activated receptor (PPAR) coactivator 1) family plays a critical role in the control of tissue-specific biological processes and in the regulation of mitochondrial oxidative metabolism (Lin et al., 2005). The PGC-1 coactivators are highly versatile, interacting with different transcription factors that directly regulate the expression of certain nuclear genes for mitochondrial products (Puigserver and Spiegelman, 2003; Kelly and Scarpulla, 2004); these include NRF-1 and NRF-2, whose genes are themselves targets of PGC-1α (Wu et al., 1999). PGC-1α and β stimulate the biogenesis of mitochondria with different metabolic characteristics, thus, by modulating the relative activity of these two coactivators, cells may achieve fine-tuning of mitochondrial function in response to specific metabolic needs (Lin et al., 2005; Feige and Auwerx, 2007).

Taken together, these data suggest that transcriptional factors and nuclear coactivators orchestrate the programs of expression of both genomes, essential to cellular energetics, therefore they can be considered main players of the communication between nucleus and mitochondria.

3. Post-transcriptional regulation

Increasing evidences demonstrate the importance of mRNA localization, stability, and translation regulation in the control of gene expression, in both developmental and differentiated cells; such regulation mostly relies upon the activity of RNA-binding proteins (Derrigo et al., 2000; Raimondi et al., 2002; Keene and Lager, 2005). The cellular activity of RNA-binding proteins is regulated by their abundance, by the availability of specific regulatory molecules and/or by post-translational modification of their binding activity (Sachs et al., 1997; Mendez et al., 2000; Dreyfuss et al., 2002). Mili and colleagues described human LRP130 protein, component of the PPR (pentatricopeptide repeat motif) group of RNA-binding proteins, which is localized both in the nucleus, where it is associated with post-splicing mRNP complexes, and in mitochondria, where it binds polyadenylated mRNAs. This suggests that LRP130 could participate in coordinating the expression of nuclear and mitochondrial genomes (Mili and Pinol-Roma, 2003). It was also found that mouse AKAP121 (kinase A anchoring protein) expressed in HeLa cells carries MnSOD mRNA in proximity of mitochondrial outer membrane, promoting its translation, thus facilitating the import into mitochondria (Ginsberg et al., 2003). Interestingly, in sea urchin embryos, we found evidence that at least one complex of 40 kDa can be formed by a region of the 3′-UTR of the hsp56 messenger RNA and a binding protein which is more abundant in the outer mitochondrial membrane (Di Liegro and Rinaldi, 2007). In addition, it was recently reported that Puf3p, a Pumilio family RNA-binding protein, localizes to mitochondria and regulates mitochondrial biogenesis in yeast (Garcia-Rodriguez et al., 2007). On the other hand, they were described factors involved in post-transcriptional regulation of mitochondrial RNAs, such as the RBP38 protein, probably implicated in RNA stabilization (Sbicego et al., 2003). In *Saccharomyces cerevisiae*, it was demonstrated that the translation and assembly of the subunits II and III of COX complex depends upon nucleus-encoded translation activators, which specifically recognize the 5′-untranslated leader of the mRNAs (Costanzo et al., 1986; Sanchirico et al., 1998). We demonstrated that, in developing rat brain, the amounts of COXIII protein and mRNA are not linearly related, suggesting that COXIII expression could also be regulated at post-transcriptional levels (Cannino et al., 2004). Recently, we described two different factors able to bind COXIII mRNA, present in the mitochondrial extracts of adult rat brain and testis, respectively. These tissue-specific factors could participate in COXIII mRNA translation and/or localization in mitochondrial inner membrane (Cannino et al., 2006). Mitochondrial extracts from rat brain also contain a factor able to bind COXIV mRNA 3′-UTR, whose binding ability decreases during brain differentiation. The same mRNA is bound by proteins present in post-mitochondrial extracts from heart, kidney, and testis. These results suggest the existence of different tissue-specific post-transcriptional regulatory factors, or the occurrence of post-translational modifications of the same factor (Cannino et al., 2006).

During liver development (Luis et al., 1993; Izquierdo et al., 1995; Izquierdo and Cuezva, 1997), in brown adipose tissue (Tvrdik et al., 1992) and in kidney cells (Di Liegro et al., 2000), the regulation of the expression of the β-subunit of the mitochondrial H^+-ATP synthase is also exerted at the level of mRNA translation. The translation of β-mRNA mostly depends on the 3′UTR of the mRNA that, interacting with the translational machinery (Izquierdo and Cuezva, 1997) and resembling internal ribosome entry sites (Di Liegro et al., 2000; Izquierdo and Cuezva, 2000), behaves as a positive regulator. In fetal liver and in hepatomas, Cuezva and colleagues found proteins that, binding to the 3′UTR of the mRNA (3′ FBPs), interfere with the translation-enhancing activity of the 3′UTR of the mRNA (Izquierdo and Cuezva, 1997; de Heredia et al., 2000), hence regulating mitochondrial biogenesis in hepatocytes (Valcarce et al., 1988; Izquierdo et al., 1995; Cuezva et al., 1997; de Heredia et al., 2000).

Since many data exist concerning the activity of RNA-binding proteins in both multicellular and unicellular systems, it is possible to hypothesize that, despite the biological differences between models, the regulation involving

protein–mRNA interactions might represent a general mechanism of the regulation of nuclear–mitochondrial interaction.

Reversible protein acetylation is emerging as a critical post-translational modification involved in the regulation of many biological processes. Although most of the pioneering experiments focused on the role of histone acetylation in transcriptional control, recent findings have generalized the concept to many non-histone proteins (Sterner and Berger, 2000). Interestingly, it was demonstrated that mammalian mitochondria contain intrinsic NAD-dependent deacetylase activity. This deacetylase is the nuclear-encoded SirT3, homologous to yeast Sir2 (Tanner et al., 2000), and it is located within mitochondrial matrix. SirT3 activity could lead to the constitutive deacetylation of one or several mitochondrial proteins (Schwer et al., 2002). SirT3 activates mitochondrial functions and plays an important role in adaptive thermogenesis, stimulating CREB phosphorylation, which directly activates PGC-1α promoter (Shi et al., 2005). Recently, it was found that, under normal cell growth conditions, SirT3 localizes not only to mitochondria, but also to the nucleus, and it is transported from the nucleus to mitochondria upon cell stress (Scher et al., 2007). SirT1, another mammalian homolog of yeast Sir2, was shown to modulate PGC-1α, leading to enhanced transcriptional activity in an NAD^+-dependent way (Rodgers et al., 2005) and, in addition, inducing a metabolic gene transcription program of mitochondrial fatty acid oxidation (Gerhart-Hines et al., 2007).

Mitochondrial activity is regulated also by modulating the import and assembly of proteins and, during the last years, several novel components of these pathways have been identified. TIM23 complex and the presequence translocase-associated motor, the PAM complex, mediate the multistep import of pre-proteins with cleavable N-terminal signal sequences into the matrix or inner membrane of mitochondria (van der Laan et al., 2006), while the inner membrane contains several components that mediate the sorting and assembly of these proteins. Together, the translocation and assembly complexes coordinate mitochondria biogenesis (Koehler, 2004). Moreover, increasing evidences indicate that chaperones participate not only in protein folding, but also in assembling and maintaining mitochondrial complexes (Szabadkai and Rizzuto, 2007). A recently discovered sorting and assembly machinery (SAM complex) is essential for integration and assembly of outer-membrane proteins (Pfanner et al., 2004). For example, the pathway of VDAC (voltage-dependent anion-selective channel) biogenesis in human mitochondria involves the TOM complex, Sam50, and metaxins. The deletion of Sam50, the central component of SAM, led to a defect in the assembly of VDAC (Kozjak-Pavlovic et al., 2007). Cytochrome *c* oxidase (COX) biogenesis includes a variety of steps from translation to the formation of the mature complex. Each step involves a set of specific factors that assist translation of subunits, their translocation across membranes, insertion of essential cofactors, assembly and final maturation of the enzyme (Khalimonchuk and Rödel, 2005). A novel gene product of the dihydrolipoamide succinyltransferase gene, MIRTD (mitochondrial respiration generator of truncated DLST), mediates the molecular assembly of the cytochrome *c* oxidase complex (COX), so that MIRTD mRNA decrease could affect energy production. The level of MIRTD mRNA is significantly low in the brains of AD (Alzheimer's disease) patients, also confirming the idea that COX defect can cause the disease (Ohta and Ohsawa, 2006).

In conclusion, different post-transcriptional and post-translational mechanisms operate in the regulation of mitochondrial biogenesis and activity. Future investigation efforts should be devoted to the understanding of the relationships between the components of these regulation systems.

4. Mitochondria to nucleus communication

Nuclear gene expression can be influenced by signals coming from mitochondria, a process called retrograde communication (Parikh et al., 1987; Liao and Butow, 1993; Poyton and McEwen, 1996; Liu and Butow, 2006), so that the regulation of mitochondrial activity depends on a bidirectional flow of information. In yeast, the retrograde signaling pathway functions as a homeostatic or stress response mechanism, to adapt various biosynthetic activities to the alterations of metabolic mitochondrial conditions (Liao et al., 1991; Small et al., 1995; Liu and Butow, 2006). Sekito and collaborators suggested a model for the control of signaling from mitochondria to nucleus, in which the cells with dysfunctional mitochondria send one or more signals to nucleus via Rtg2p: the dephosphorylation of a highly phosphorylated form of Rtg3p leads to its transient dissociation from Rtg1p and to the translocation of Rtg1p and Rtg3p to the nucleus. Here they bind the GTCAC box sites of target genes and consequently activate transcription (Sekito et al., 2000). In skeletal mammalian myoblasts and in human pulmonary carcinoma cells, mitochondrial retrograde signaling seems to occur through cytosolic $[Ca^{2+}]_i$ changes (Biswas et al., 1999; Amuthan et al., 2002). The alteration of mitochondrial membrane potential ($\Delta\Psi$) reduces mitochondrial Ca^{2+} uptake and, in turn, it reduces ATP availability, causing reduction of calcium efflux into storage organelles or outside the cells. Increased cytosolic Ca^{2+} concentration in turn activates calcineurin, and related factors such as Ca^{2+}-dependent kinases, causing the activation of different nuclear transcription factors (Butow and Avadhani, 2004). Interestingly, the absence of mitochondrial function blocks myotube differentiation, probably through the specific down-regulation of myogenin mRNA transcription (Rochard et al., 2000). The retrograde signaling could be realized by the translocation of some mitochondrial proteins to the cytoplasm, and/or into the nucleus.

According to such hypothesis, we recently found that, in developing rat brain, cytochrome *c* oxidase subunit III is localized not only in mitochondria, but is also present in the cytosol (Cannino et al., 2004), where it could exert a regulatory role.

Even if these data were obtained in different systems and the molecular mechanisms so far described are different, one can look at retrograde communication as a common necessary mechanism modulating nuclear–mitochondrial interaction.

5. Mitochondria and cancer

Genetic and/or epigenetic alterations of mitochondrial functions cause a large variety of degenerative diseases, aging, and cancer (Wallace, 1999; Brandon et al., 2006; Singh, 2006). An expanding number of autosomal diseases were associated with mitochondrial DNA depletion and multiple deletions. These disorders are due to defects of intergenomic communication, in fact mutations of nuclear genes for mitochondrial proteins possibly disrupt the normal cross-talk that regulates the number of mtDNA copies and expression of mitochondrial genes, as suggested by Hirano and Vu (2000).

An association between mitochondrial dysfunction and cancer was made by Otto Warburg, (1930) and metabolic aberrations associated with mitochondrial bioenergetic functions in cancer cells were observed (Modica-Napolitano et al., 2007). The relationship between mitochondrial disorders and mutations was documented for several dozens of nuclear genes encoding proteins directly or indirectly involved in the biogenesis of the respiratory chain complexes (Rötig and Munnich, 2003). Most human carcinomas express reduced amounts of the catalytic subunit of H^+-ATP synthase (Santamaría et al., 2006). In contrast, the expression of nuclear encoded cytochrome *c* oxidase subunits increases in human prostate carcinoma (Herrmann et al., 2003). Indeed, mutant mtDNA in tumor cells is more abundant than mutated nuclear marker (Fliss et al., 2000), so that mtDNA mutations were used as clonal markers in hepatocellular carcinoma (Nomoto et al., 2002) and breast cancer (Parrella et al., 2001). Interestingly, mitochondrial disfunction resulting from changes in mtDNA invokes mitochondria-to-nucleus retrograde responses in human cells (Modica-Napolitano et al., 2007). Kulawiec and colleagues, using a proteomic analysis, compared a cell line missing mitochondrial genome and a cybrid cell line in which mtDNA had been restored. They demonstrated changes in the expression of several proteins, and suggested that retrograde responsive genes may potentially function as tumor suppressor or oncogenes (Kulawiec et al., 2006). These studies show the correlation between functional defects of mitochondria and tumorigenesis, and suggest that retrograde signaling may be an important factor in restoring the non-tumorigenic phenotype (Modica-Napolitano et al., 2007).

6. Concluding remarks

Mitochondrial function must rely on an orchestrated cross-talk between nuclear and mitochondrial genes and, although the genomes are physically distinct, they should be considered interdependent from the functional point of view. In this review, we discuss the communication between nucleus and mitochondria and the mechanisms that could regulate this complex interplay. From the above-mentioned works, it appears clear that nucleus has a dominant role in the regulation of mitochondrial activity. Nuclear-coded transcriptional factors control the activity of mitochondrial genome, coordinating the expression of both nuclear and mitochondrial genes for mitochondrial proteins. In addition, nucleus activity makes use of proteins that regulate translation, stability, and localization of the mRNAs, both of nuclear and mitochondrial origin, modulating developmental and/or tissue-specific expression. RBPs' activity could represent a mechanism involved in the nucleus to mitochondrion communication. Other nucleus-encoded proteins participate in the control of the import of mitochondrial proteins and ensure the correct assembly of OXPHOS complexes. The coordination between transcriptional and post-transcriptional regulation mechanisms might be due to ''compensation'' factors, responsible for the regulation of respiratory enzymes synthesis, according to the requirements of subunits assembly in fully functioning complexes. Nonetheless, nuclear gene expression can be influenced by signals coming from mitochondria, through retrograde communication, so that the regulation of mitochondrial activity requires a bidirectional flow of information.

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