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Review

Regulation of mammalian mitochondrial translation by post-translational modifications☆,☆☆

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ABSTRACT

Mitochondria are responsible for the production of over 90% of the energy in eukaryotes through oxidative phosphorylation performed by electron transfer and ATP synthase complexes. Mitochondrial translation machinery is responsible for the synthesis of 13 essential proteins of these complexes encoded by the mitochondrial genome. Emerging data suggest that acetyl-CoA, NAD^+, and ATP are involved in regulation of this machinery through post-translational modifications of its protein components. Recent high-throughput proteomics analyses and mapping studies have provided further evidence for phosphorylation and acetylation of ribosomal proteins and translation factors. Here, we will review our current knowledge related to these modifications and their possible role(s) in the regulation of mitochondrial protein synthesis using the homology between mitochondrial and bacterial translation machineries. However, we have yet to determine the effects of phosphorylation and acetylation of translation components in mammalian mitochondrial biogenesis. This article is part of a Special Issue entitled: Mitochondrial Gene Expression.

1. Introduction

Oxidative phosphorylation (OXPHOS) in mitochondria is responsible for providing over 90% of the ATP used by mammalian cells. Generation of a proton gradient across the inner membrane of the mitochondria is essential for ATP synthesis. The translocation of protons across the inner membrane is highly regulated and facilitated by hydrophobic proteins of the electron transfer complexes embedded in the inner membrane of mitochondria to prevent proton leakage. Mitochondria, the ancient endosymbiotic bacteria, have retained a small (16,568 bp) circular mitochondrial genome, unique transcription and translation machineries to synthesize these extremely hydrophobic proteins of the electron transfer complexes and ATP synthase (Fig. 1). Human mitochondrial DNA (mtDNA) also encodes 22 tRNAs and two rRNAs that are required for the synthesis of these hydrophobic proteins. Although a majority of the OXPHOS subunits are imported from the cytosol, mitochondria rely on their own ribosomes and translation machinery to produce the 13 hydrophobic proteins of the electron transfer complexes in order to support ATP synthesis.

The evolutionarily conserved bacterial and mitochondrial translation processes are elegantly described by Christian and Spremulli in the previous section [1]. As the homology of their protein components show, mammalian mitochondrial ribosomes resemble bacterial ribosomes more so than eukaryotic cytoplasmic ribosomes. Mitochondrial ribosomes have a low sedimentation coefficient of ~55S and consist of 28S and 39S subunits [2]. All mammalian mitochondrial ribosomal proteins (MRPs) are encoded by nuclear genes and imported into mitochondria where they are assembled into ribosomes with mitochondrially encoded small (12S) and large (16S) rRNAs [3,4]. A careful analysis of the secondary structures of the bacterial and mitochondrial rRNAs shows that the smaller mitochondrial rRNAs are not randomly shortened. The regions that are missing in 12S and 16S mitochondrial rRNAs tend to be on the periphery of the three-dimensional space occupied by the bacterial 16S and 23S rRNAs [5,6]. The mammalian mitochondrial ribosome contains 29 proteins in the small subunit whereas the large subunit consists of 50 proteins [7–11]. About half of these proteins have homologs in bacterial ribosomes while the remainder of these proteins represents a new class of ribosomal proteins specific to mitochondria. The homologous MRPs are larger than their bacterial counterparts, and due to the increased number of proteins and shortened rRNAs, mammalian mitochondrial ribosomes can be described as “protein-rich” ribosomes (Table 1) [8,10,12]. During the evolution of mitochondria from endosymbiotic bacteria, this high protein/shortened rRNA arrangement was probably favored to protect rRNA from the oxidative environment of the mitochondria, as RNA is more prone to oxidative damage than proteins.

The distribution of mitochondria-specific proteins on the exterior surface of the ribosome was visible in the cryo-EM studies; however, additional high-resolution structural information is still needed to determine their exact function in translation [12]. Our studies suggest that bacterial 70S ribosomal proteins with no clear homologs are replaced by mitochondria-specific proteins in the mitochondrial

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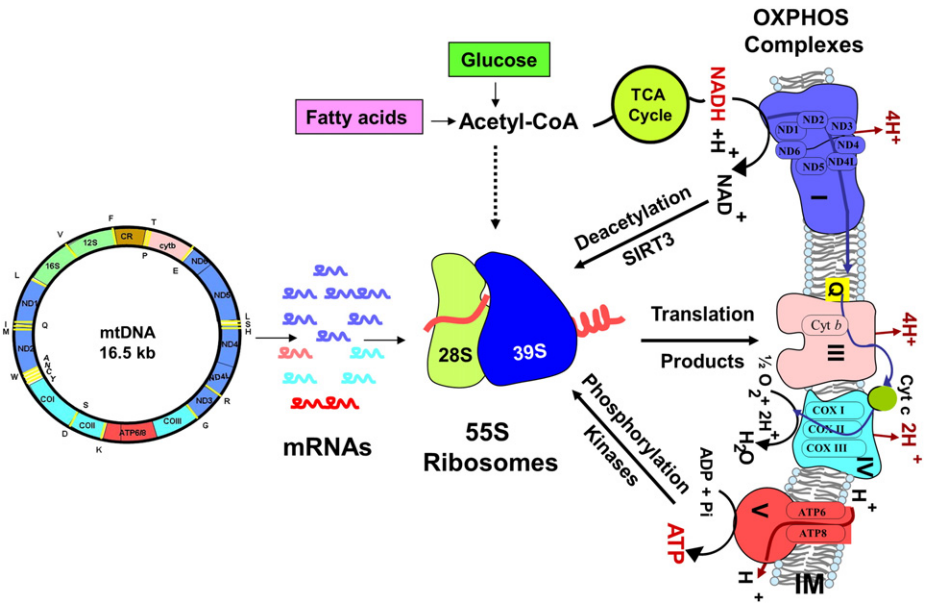

Fig. 1. Oxidative phosphorylation and regulation of the mitochondrial translation machinery. Mammalian mitochondria contain a 16.5 kb circular genome (mtDNA) which encodes for 22 tRNAs, two rRNAs, and 9 monocistronic and 2 dicistronic mRNAs. Mammalian mitochondrial ribosomes (28S and 39S subunits) are responsible for the synthesis of 13 mitochondrial encoded subunits of the Complex I (blue), III (pink), IV (cyan) and ATP synthase (Complex V). Metabolic levels of acetyl-CoA, NADH/NAD^+ and ATP are important for the regulation of the mitochondrial translation machinery by reversible acetylation and phosphorylation.

ribosome (Table 1 and Fig. 2) [8–10]. Several of these proteins have acquired extra-ribosomal activities. For example, four mitochondria-specific MRPs, MRPS29 (Death Associated Protein 3-DAP3), MRPS30 (Programmed Cell Death Protein 9-PDCD9), MRPL37, and MRPL41, were both identified as mitochondria-specific MRPs, and MRPS30, were found to be involved in apoptosis [13–17]. Additionally, Immature Colon Carcinoma Transcript-1 (ICT1) is a *bona-fide* member of the ribosome involved in the peptidyl-tRNA hydrolase activity [18].

Although half of these MRPs have no homologs in bacteria, the majority of the functional regions of bacterial ribosomes are conserved in mitochondrial ribosomes to support the peptidyl transferase activity, mRNA and tRNA recruitment, decoding, and translocation during the initiation and elongation stages [12,19–22]. Major conformational changes of these highly conserved functional regions is also induced by GTP hydrolysis and thermal fluctuations during the different stages of translation; however, accumulating data suggests that more subtle and localized effects on protein–protein and protein–RNA interactions could be caused by post-translational modifications (PTMs) of ribosomal proteins [23–30]. Two such modifications, phosphorylation and acetylation, are believed to affect different stages of protein synthesis by modulating mRNA/tRNA and factor binding to ribosomes. Therefore, it is possible that the protein-rich surface of the mitochondrial ribosome provides both the protection of rRNA and the efficient modulation of protein synthesis in response to metabolic changes and the fluctuating energy demands of an organism.

Table 1
Comparison of mammalian mitochondrial and bacterial ribosomes.

	Prokaryotic	Mitochondrial
Sedimentation coefficient	70S	55S
Subunits	30S and 50S	28S and 39S
Small subunit proteins	21 (S1–S21)	29 (MRPS2–MRPS36)[a]
Large subunit proteins	L1–L36	50 (MRPL1–MRPL57)[a]
Small subunit rRNA	16S (1542nt)	12S (950nt)
Large subunit rRNA	23S (2904nt), 5S (120nt)	16S (1560nt)
RNA/protein ratio	1:2	2:1

[a] The homologs of bacterial ribosomal small subunit proteins, S1, S3, S4, S8, S13, S19, and S20, and large subunit proteins, L5, L6, L25, and L31, are not found in the 55S ribosome.

2. Protein phosphorylation and acetylation in mitochondria

The main cellular function of mitochondria is the production of ATP. ATP is produced by oxidation of acetyl-coA and several other metabolites in the TCA cycle and OXPHOS. Reversible phosphorylation and acetylation tightly regulate these processes leading up to energy production, including mammalian mitochondrial translation machinery that is responsible for the synthesis of mitochondrially-encoded components of OXPHOS complexes (Fig. 1) [31–34].

Phosphorylation of proteins is the most common and one of the best-understood signaling mechanisms that regulate and connect many metabolic pathways in eukaryotes. This modification is catalyzed by kinases that use ATP as a substrate. For example, the transfer of phosphoryl groups ($-HPO_3^{2-}$) to Ser, Thr, and Tyr residues generates negatively charged side chains, which significantly changes the structural properties of these amino acid residues. More generally, the activities of many mitochondrial enzyme complexes are tightly regulated by phosphorylation, catalyzed by specific kinases associated with these complexes, to make the process more efficient [35–37].

Concurrently, recent data suggests that reversible acetylation is critical for regulation of energy metabolism in mammalian mitochondria [33,38,39]. Over 30% of the mitochondrial proteins/enzymes involved in oxidative metabolic pathways, such as fatty acid oxidation, amino acid oxidation, the TCA cycle, and the urea cycle, have been shown to be acetylated [40–44]. Acetylation neutralizes positive charges on ε-amino groups of lysine residues and usually results in the inhibition of metabolic enzyme activities, including the activities of glutamate dehydrogenase, long chain fatty acid dehydrogenase, and nuclear encoded subunits of the electron transport chain complexes, Complex I and II [45–47].

Despite intensive studies aimed toward the identification of acetyltransferases in mammalian mitochondria, no protein acetyltransferase activity has been detected to date. On the other hand, several members of the class III histone deacetylases sirtuins (homologs of the yeast *Sir*2 gene, silent mating type information regulation 2), have been found to reside in mitochondria [48–53]. The mitochondrial sirtuins (SIRT3, SIRT4 and SIRT5) are vital for cell survival and act in a NAD^+-dependent manner, using NAD^+ as a co-substrate in deacetylation and ADP-ribosylation reactions [53]. However, SIRT3