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Review

Control of protein synthesis in yeast mitochondria: The concept of translational activators ☆

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ABSTRACT

Mitochondria contain their own genome which codes for a small number of proteins. Most mitochondrial translation products are part of the membrane-embedded reaction centers of the respiratory chain complexes. In the yeast *Saccharomyces cerevisiae*, the expression of these proteins is regulated by translational activators that bind mitochondrial mRNAs, in most cases to their 5′-untranslated regions, and each mitochondrial mRNA appears to have its own translational activator(s). Recent studies showed that these translational activators can be part of feedback control loops which only permit translation if the downstream assembly of nascent translation products can occur. In several cases, the accumulation of a non-assembled protein prevents further synthesis of this protein but not translation in general. These control loops prevent the synthesis of potentially harmful assembly intermediates of the reaction centers of mitochondrial enzymes. Since such regulatory feedback loops only work if translation occurs in the compartment in which the complexes of the respiratory chain are assembled, these control mechanisms require the presence of a translation machinery in mitochondria. This might explain why eukaryotic cells maintained DNA in mitochondria during the last two billion years of evolution. This review gives an overview of the mitochondrial translation system and summarizes the current knowledge on translational activators and their role in the regulation of mitochondrial protein synthesis. This article is part of a Special Issue entitled: Protein import and quality control in mitochondria and plastids.

1. Introduction

Eukaryotic cells of animals and fungi contain two translation machineries, one in the cytosol and one in mitochondria. The cytosolic translation system is well studied whereas we know little about the mitochondrial translation system. This is in part due to the fact that early studies claimed, on the basis of the sedimentation constant of the mitochondrial ribosome and its sensitivity to antibiotics, that the mitochondrial translation system is essentially identical to that of prokaryotes [1–3]. Hence studies on the mitochondrial system were expected to be unrewarding as they would only confirm what had previously been found on the bacterial translation system. However, more detailed analysis of the mitochondrial translation system shows that it differs significantly from that of bacteria. Moreover, the absence of a reconstituted system that would allow the synthesis of mitochondrial translation products *in vitro* largely prevented a detailed analysis of the mechanisms by which proteins are synthesized in mitochondria. Over the last decades genetic screens for petite (respiration-deficient) yeast mutants identified many factors from *Saccharomyces cerevisiae* that are critical for the expression of mitochondrial proteins. A subgroup of these mutants showed specific translation defects in which the synthesis of individual mitochondrially encoded proteins is affected [4–7]. The analysis of these mutants led to the concept of translational activators, *i.e.* components that interact with specific mitochondrial mRNAs to facilitate their translation by the ribosome [8–11]. Although potential translational activators could be identified for all protein genes of the mitochondrial genome of *S. cerevisiae* (Table 1), their molecular function in translational initiation or elongation is still largely unclear. It is also unclear whether all translational activators bind directly to mRNA sequences or whether some of them interact with other components of the translation machinery. Interestingly, recent studies showed that translational activators control the level of mitochondrial protein synthesis and adapt the amount of the proteins that are produced to the efficiency of their assembly processes. Thereby, translational activators prevent the accumulation of non-assembled translation products which, due to their activity in electron or proton transport, can be highly deleterious for the cell [12–14]. This review will be focused on mRNA-specific translational activators from the budding yeast *S. cerevisiae* and only briefly present similar factors from other species, like the fission yeast *Schizosaccharomyces pombe* and human.

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2. The mitochondrial translation system

The number of mitochondrially encoded proteins is very small compared to the total number of mitochondrial proteins: in 2009, the manually validated list of mitochondrial proteins of the MitoP2 database showed 590 entries for yeast, 920 for human and 1020 for mouse [15]. Proteomic studies on the basis of mass spectrometry of mitochondria isolated from mouse tissues led to the identification of 3881 different proteins [16]. Even if a fraction of these proteins might be due to contamination of the samples this large number is surprising since this suggests that mitochondria of eukaryotic cells are more complex than many bacteria. The genome of *Rickettsia prowazekii*, which was suggested to be closely related to the endosymbiotic ancestor of mitochondria, contains only 834 protein-coding genes [17]. Despite this large number of mitochondrial proteins, mitochondrial genomes are small and encode only a handful of proteins. The largest mitochondrial genomes are found in some protists and plants where up to 67 proteins can be encoded [18–21]. At the other extreme, there are some parasites like *Plasmodium falciparum* where the mitochondrial genome codes for only three proteins. Most animals and fungi have mitochondrial genomes that code for a similar set of about a dozen products which all are hydrophobic proteins and which constitute the membrane-embedded reaction centers of complexes I, III, IV and V of the respiratory chain. All other genes of the bacterial ancestor of mitochondria were either lost or transferred to the nuclear genome. Why the remaining genes were not transferred is unclear. It was speculated that the hydrophobicity of these components would prevent their import from the cytosol to the inner membrane of mitochondria ("hydrophobicity argument") [22,23]. A second, and not mutually exclusive explanation is that mitochondrial expression of these proteins allows a coordinated synthesis and assembly in the organelle ("regulation argument"). There is compelling experimental evidence for both arguments; the mechanisms by which translation efficiency is coupled to complex assembly is discussed in Section 4.

2.1. Mitochondrial ribosomes

Mitochondrial ribosomes of *S. cerevisiae* have a sedimentation coefficient of 74 S [24]. The small subunit (37 S) consists of a *15S* rRNA and at least 34 proteins, the large subunit (54 S) contains a *21S* rRNA and at least 44 proteins ("*Saccharomyces* Genome Database" http://www.yeastgenome.org/ Dec. 2011) [25–27]. About half of the ribosomal proteins have bacterial homologs but many of these conserved components were significantly changed during evolution; most of these proteins have N- or C-terminal extensions whose function is not clear [25,28,29].

Published information on the structure of fungal ribosomes does not exist, but cryo-electron microscopic analyses of mitochondrial ribosomes of animals and protists revealed big structural differences when compared to the cytosolic ribosomes of bacteria or eukaryotes [30,31]. These differences were most obvious for the surface of the ribosome (which is largely protein-covered in mitochondria) whereas the catalytic region at the interface of both subunits appeared to be largely conserved [29,32]. Interestingly, the region around the polypeptide exit tunnel differed considerably from that of other ribosomes probably due to the interaction of the mitochondrial ribosomes with the protein insertion machinery of the inner membrane [30]. Yeast mitochondrial ribosomes are indeed permanently tethered to the inner membrane,

Table 1
Translational activators of *S. cerevisiae* and potential homologs in fungi and humans.

Regulated gene	Translational activator	*Z. rouxii*	*A. gossypii*	*C. glabrata*	*K. lactis*	*Y. lipolytica*	*N. crassa*	*S. pombe*	*H. sapiens*
VAR1	Sov1	34.6 (56.0) XP_002498989	27.1 (46.7) NP_984245	29.5 (47.9) XP_446255	25.7 (44.5) XP_456240	17.3 (32.3) XP_504517.1	n.d.	n.d.	n.d.
COB	Cbs1	23.2 (40.8) XP_002495492.1	19.5 (36.3) NP_984926.1	27.7 (38.2) XP_445445.1	22.2 (36.6) XP_451676.1	n.d.	n.d.	n.d.	n.d.
	Cbs2[a]	38.7 (59.0) XP_002495851.1	25.1 (47.0) NP_986558.1	27.2 (47.1) XP_446211.1	33.7 (54.5) XP_453891.1	22.4 (37.6) XP_505684.1	16.9 (30.2) XP_962957.1	23.6 (39.2) NP_596855.1	n.d.
	Cbp1	39.0 (58.2) XP_002496426.1	n.d.	25.9 (44.3) XP_447525.1	n.d.	14.2 (29.1) XP_504853.1	n.d.	n.d.	n.d.
	Cbp3	67.5 (78.4) XP_002499238.1	65.5 (77.4) NP_985439.2	59.9 (70.1) XP_445942.1	60.3 (73.5) XP_451625.1	34.3 (47.7) XP_501967.1	22.3 (33.8) XP_955800.1	31.4 (41.4) NP_588073.1	21.0 (31.5) AAL13118.1
	Cbp6	58.9 (77.9) XP_002496369.1	55.2 (72.4) NP_983724.1	53.0 (75.6) XP_445464.1	55.8 (76.7) XP_451927.1	15.1 (26.8) XP_002142985.1	22.4 (37.1) XP_956065.1	17.8 (32.5)[b] NP_595262.1	15.8 (26.7)[b] NP_115716.1
COX1	Pet309	44.6 (65.5) XP_002497313.1	28.8 (50.7) NP_983174.1	34.3 (55.3) XP_446040.1	32.3 (53.7) XP_453302.1	13.8 (24.2) XP_499812.1	16.5 (31.7) XP_961771.1	17.0 (30.7) NP_594277.1	14.4 (21.1) AAA67549.1
	Mss51	70.7 (81.7) XP_002497704.1	64.3 (74.6) NP_983252.1	69.2 (78.1) XP_444937.1	69.4 (81.0) XP_453616.1	55.6 (71.1) XP_504687.1	31.5 (43.2) XP_957281.2	33.0 (48.2) NP_594464.1	17.8 (31.8)[c] NP_001019764.1
COX2	Pet111	32.7 (54.8) XP_002498568.1	23.1 (38.7) NP_986449.1	24.8 (49.3) XP_446903.1	21.7 (45.6) XP_451913.1	n.d.	n.d.	n.d.	n.d.
COX3	Pet54	34.9 (52.3) XP_002495605.1	26.5 (43.8) NP_983963.2	30.0 (47.3) XP_445062.1	28.9 (45.6) XP_454667.1	n.d.	n.d.	n.d.	n.d.
	Pet122	27.2 (46.6) XP_002495426.1	20.9 (35.5) NP_986808.1	29.0 (44.5) XP_447535.1	19.9 (36.9) XP_453991.1	n.d.	n.d.	n.d.	n.d.
	Pet494	30.9 (48.5) XP_002497187.1	23.2 (41.5) NP_986428.2	31.4 (48.0) XP_445331.1	25.6 (45.3) XP_454026.1	n.d.	n.d.	n.d.	n.d.
ATP6/8	Atp22	32.3 (54.8) XP_002494650.1	22.9 (43.5) NP_983301.1	27.7 (45.5) XP_444871.1	21.4 (39.4) XP_454934.1	n.d.	n.d.	n.d.	n.d.
ATP9	Aep1/Nca1	25.1 (41.1) XP_002498995.1	19.7 (36.3) NP_984238.1	23.2 (43.2) XP_446253.1	22.0 (42.0) XP_456247.1	n.d.	n.d.	n.d.	n.d.
	Aep2/Atp13	25.0 (40.9) XP_002498605.1	19.8 (37.6) NP_982828.2	24.7 (40.3) XP_449480.1	23.1 (40.8) XP_453131.1	n.d.	n.d.	15.7 (26.9)[b] NP_588200.1	n.d.

Potential homologs were identified using reciprocal PSI-BLAST [142] searches with the *S. cerevisiae* sequences. After alignments with the *S. cerevisiae* sequences, identity (and similarity) values were determined. Homologs were searched in the genomes of *Ashbya gossypii*, *Candida glabrata*, *Homo sapiens*, *Kluyveromyces lactis*, *Neurospora crassa*, *Schizosaccharomyces pombe*, *Yarrowia lipolytica*, and *Zygosaccharomyces rouxii*.

[a] Cbs2 has a homolog in *S. cerevisiae* named Pan5, which is not involved in mitochondrial biogenesis. The sequences retrieved in *Y. lipolytica*, *N. crassa* and *S. pombe* are significantly closer to Pan5 than to Cbs2 by reciprocal Blast searches, suggesting that the actual Cbs2 protein is probably not conserved in these three organisms.

[b] According to Kühl et al. [133,134].

[c] According to Perez-Martinez et al. [120].