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Review

Supernumerary proteins of mitochondrial ribosomes ☆

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ABSTRACT

Background: Messenger RNAs encoded by mitochondrial genomes are translated on mitochondrial ribosomes that have unique structure and protein composition compared to prokaryotic and cytoplasmic ribosomes. Mitochondrial ribosomes are a patchwork of core proteins that share homology with prokaryotic ribosomal proteins and new, supernumerary proteins that can be unique to different organisms. In mammals, there are specific supernumerary ribosomal proteins that are not present in other eukaryotes.
Scope of review: Here we discuss the roles of supernumerary proteins in the regulation of mitochondrial gene expression and compare them among different eukaryotic systems. Furthermore, we consider if differences in the structure and organization of mitochondrial genomes may have contributed to the acquisition of mitochondrial ribosomal proteins with new functions.
Major conclusions: The distinct and diverse compositions of mitochondrial ribosomes illustrate the high evolutionary divergence found between mitochondrial genetic systems.
General significance: Elucidating the role of the organism-specific supernumerary proteins may provide a window into the regulation of mitochondrial gene expression through evolution in response to distinct evolutionary paths taken by mitochondria in different organisms. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction

Mitochondrial genomes encode a limited set of mRNAs that are translated on mitochondrial ribosomes to produce specific protein subunits of the oxidative phosphorylation (OXPHOS) complexes. Mitochondrial ribosomes are composed of rRNAs that are encoded by the mitochondrial genome and ribosomal proteins that are typically encoded by the nuclear genome and imported post-translationally into mitochondria. Mitochondrial genomes in some fungi, plants and protists also encode several ribosomal proteins. Mitochondria encode either a complete set of tRNAs within their genomes or import some of their tRNAs from the cytoplasm that are required for translation by mitochondrial ribosomes. The composition of mitochondrial ribosomes can vary between different organisms, and it is likely that the size and organization of mitochondrial genomes have necessitated the acquisition of new domains and proteins within the ribosome. Here we briefly summarize the knowledge about mitochondrial ribosomes, since a detailed description of the composition and structure of mitochondrial ribosomes has been covered recently [1–4]. Instead we focus on the known and suspected roles of the supernumerary and mammalian specific ribosomal proteins identified to date. Finally, we present the knowledge gained about the role of the mammalian specific ribosomal proteins from human diseases caused by mutations in the genes encoding these proteins.

2. Mitochondrial ribosomes

Mitochondrial ribosomes are located inside the matrix, the site of the transcriptome, and they closely associate with the mitochondrial inner membrane to allow co-translational insertion of the hydrophobic proteins into the inner membrane followed by their assembly into the OXPHOS complexes [5]. The mitochondrial ribosome is composed of over 80 proteins and two rRNAs that make up the small and large ribosomal subunits [1,3,6–10]. Mitochondrial ribosomal RNA has reduced in size considerably during evolution and has been replaced by additional proteins. These proteins share homology with cytoplasmic ribosomal proteins from prokaryotes and yeast and some of them are unique to mitochondrial ribosomes. Mitochondrial ribosomal proteins that have conserved rRNA-binding sites have been observed to be similar in size to those in *Escherichia coli* ribosomes, and ribosomal proteins whose binding sites on rRNA are shortened or lost, carry N- or C-terminal extensions [1]. Although it has been suggested that an increased ribosomal protein content may compensate for the loss of rRNA, it has been shown that many of these additional ribosomal proteins do not replace the missing RNA helices but instead have unique positions, decorating the exterior of the mitochondrial ribosome [1,11]. One example is the loss of the 3′ end of the mitochondrial small subunit rRNA, which contains

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the message-binding site (MBS) in bacterial rRNA and recruits mRNAs for translation initiation. This is perhaps not surprising, given that mitochondrial mRNAs do not have the characteristic ribosome-binding sequences (RBS) that directly base pair with the MBS, however how ribosomal proteins can compensate for this loss and ensure accurate start codon recognition is not currently understood. About 20% of mitochondrial ribosomal proteins replace the rRNA helices that are lacking in mitochondrial ribosomes, however in the mitochondrial protist *Leichmania* ribosomes more than 50% of the missing rRNA helices are replaced by proteins [9,12]. The mRNA decoding and peptide-bond forming active sites in the small and large ribosomal subunits are composed of conserved rRNA helices, although it has been observed that there is higher protein abundance around these sites compared to cytoplasmic or prokaryotic ribosomes [1]. The significance of the supernumerary proteins and the extended domains of the conserved proteins is unclear. It is suggested that the organization of the mitochondrial genomes in different organisms has driven the evolution of the diversity in mitochondrial ribosomal proteins.

A heterogeneous complement of proteins has been observed in prokaryotic as well as cytoplasmic ribosomes of eukaryotes [13–15], however whether this is the case for mitochondrial ribosomes remains to be determined. There is some notion that there may be heterogeneous ribosomes through the discovery of three different isoforms of MRPS18, however this remains to be determined experimentally. Changes in the expression of ribosomal proteins, including mitochondrial ribosomal proteins, have been observed between different organisms, developmental stages and growth conditions, possibly reflecting specific requirements for translation [16–22].

3. Supernumerary ribosomal proteins in mitochondria

The additional proteins found in mitochondrial ribosomes do not share homology with bacterial and cytoplasmic ribosomal proteins, although some have homology between yeast and animal mitochondria and some are unique to specific organisms such as in *Leishmania* and yeast mitochondria [8,23]. Recently, 95 additional supernumerary proteins have been identified in mitochondrial ribosomes from *Trypanosoma brucei* that are unique to kinetoplastids [24], although their functions are not known. In contrast, there are fewer yeast specific supernumerary proteins compared to those found in humans, and some of these are transcript specific regulators of translation (Tables 1 and 2). Clearly organism specific supernumerary proteins have unique roles within their mitochondrial ribosomes. In archea, ribosomes have lost proteins in contrast to eukaryotic mitochondrial ribosomes that have acquired additional proteins [23]. It has been suggested that the composition of mitochondrial ribosomes in different organisms is still rapidly evolving, unlike that of cytoplasmic and bacterial ribosomes [8,23,25].

The mammalian mitochondrial ribosome is composed of large 39S and small 28S subunits that associate and sediment as 55S particles [26,27]. Mammalian mitochondrial ribosomes have only two rRNAs encoded by the mitochondrial genome, the small subunit 12S rRNA and the large subunit 16S rRNA [28]. In addition to the core ribosomal proteins that share homology with prokaryotic ribosomes, human mitochondrial ribosomes have 35 supernumerary proteins, some of which may have new functions in mitochondrial translation and recognition of mitochondrial mRNAs within the small and large ribosomal subunits [1].

Table 1
Supernumerary ribosomal proteins of the small mitochondrial subunit.

Human MRP	Yeast MRP	Present in last common eukaryotic ancestor?[a]	Homologous domains	Role in mitochondria
MRPS22				Genetic defects result in combined oxidative phosphorylation deficiency [61] and Cornelia de Lange-like dysmorphic features [64].
MRPS23	Rsm25			
MRPS25	Mrp49		NDUFB8	Not essential for translation in yeast [65].
MRPS26			Coiled coil	
MRPS27			Pentatricopeptide repeats (PPRs)	Required for translation [36].
MRPS28				
MRPS29	Rsm23		Death associated protein 3 (DAP3)	Promotes apoptosis [31,34,66], Binds GTP and is phosphorylated [67]. Cross-links to mitochondrial translational initiation factor 3 (IF3(mt)) [2]. Associates with NOA1 and Complex I [30].
MRPS30			PDCD9/MRPL37	Promotes apoptosis [32,34,68].
MRPS31				Autoantigen in type 1 diabetes [69].
MRPS32				Identical to MRPL42. Cross-links to mitochondrial translational initiation factor 3 (IF3(mt)) [2].
MRPS33	Rsm27			Heterozygous deletion causes cardiomyopathy in flies [41].
MRPS34				
MRPS35	Rsm24			
MRPS36	Ymr31			Cross-links to mitochondrial translational initiation factor 3 (IF3(mt)) [2].
PTCD3			PPRs	Required for translation [37]. Cross-links to mitochondrial translational initiation factor 3 (IF3(mt)) [2]. Associates with TEFM [40].
	Rsm22		rRNA methyltransferase	
	Ppe1			
	Mrps35			
	Mrp51			Genetic interactions with mutations in the COX2 and COX3 mRNA 5′-UTRs in yeast [45].
	Mrp13			
	Mrp1			Genetic interaction with PET122, a COX3-specific translational activator, in yeast [46].
	Rsm26		Superoxide dismutase (SOD)	
	Pet123		Coiled coil	Genetic interaction with PET122, a COX3-specific translational activator, in yeast [46].
	Mrp10		COX19, NDUFA8	
	Rsm28		Kinase	Genetic interactions with mitochondrial translation initiation factor 2 (IF2) and the methionyl-tRNA-formyltransferase (FMT1) suggest a role in translation initiation in yeast [47].
	Mrp8			

[a]The supernumerary proteins present in the last common eukaryotic ancestor are shaded in gray [64,65,66,67,68,69].

3.1. Supernumerary proteins of the small ribosomal subunit

The mitochondrial small ribosomal subunit is responsible for mRNA recruitment, association with initiation factors and mRNA decoding [15]. The small subunit of mammalian ribosomes is composed of 29 proteins, of these 14 are core ribosomal proteins that share homology with prokaryotic ribosomal proteins and 15 are unique proteins (Table 1). Some progress has been made to elucidate the role of supernumerary proteins, however a confounding factor to the identification of their functions within the mitochondrial ribosome is the lack of a robust *in vitro* mitochondrial translation system. One of the unusual features of mitochondrial ribosomes is the presence of a GTP binding protein in the small ribosomal subunit. This is the mammalian supernumerary protein MRPS29 that is located adjacent to the interface between ribosomal subunits, hypothesized to be the binding site of mitochondrial initiation factor 3 (IF3mt) [2]. MRPS29 has been found to associate

Table 2
Supernumerary ribosomal proteins of the large mitochondrial subunit.

Human MRP	Yeast MRP	Present in last common eukaryotic ancestor?[a]	Functional domains	Role in mitochondria
MRPL37			PDCD9/MRPS30	
MRPL38	Mrpl35		Phosphatidylethanolamine-binding protein 1 (PEBP-1)	
MRPL39			Threonyl-tRNA synthetase	
MRPL40	Mrpl28			May contribute to Velo-cardio-facial syndrome [70].
MRPL41	Mrpl27			Bcl-2 binding protein, promotes apoptosis [50,71]. Located close to the polypeptide exit channel of the ribosome [49].
MRPL42				Identical to MRPS32. Cross-links to mitochondrial translational initiation factor 3 (IF3(mt)) [2].
MRPL43	Mrpl51		NDUFB8	
MRPL44	Mrpl3		Ribonuclease III	Located close to the polypeptide exit channel of the ribosome [49]. Mutation causes mitochondrial infantile cardiomyopathy [63].
MRPL45	Mba1		Tim44	Located close to the polypeptide exit channel of the ribosome [49]. Possible role in protein insertion into the inner membrane [5].
MRPL46	Mrpl17/Mrpl30		Nudix	
MRPL48			Rps10	Cross-links to the mitochondrial inner membrane protein Oxa1L [72].
MRPL49	Img2			Cross-links to the mitochondrial
				inner membrane protein Oxa1L [72].
MRPL50				
MRPL51				Cross-links to the mitochondrial inner membrane protein Oxa1L [72].
MRPL52				
MRPL53	Mrpl44			
MRPL54	Mrpl37			
MRPL55			Kyrpides, Ouzounis, Woese-motif (KOW-like motif)	Required for development in flies [53].
MRPL56			Beta-lactamase	
ICT1			Peptidyl-tRNA hydrolase	Possible role in the hydrolysis of prematurely terminated peptidyl-tRNAs in stalled mitochondrial ribosomes [38].
C7orf30			Domain of unknown function 143 (DUF143)	Required for translation [73,74]. Interacts with MRPL14 [73].
	Mrpl13			Located close to the polypeptide exit channel of the ribosome [49].
	Mrpl15			
	Mrpl20		Mesenchymal stem cell protein	
	Mrpl25			Deletion confers increased longevity in yeast [58].
	Mrpl31			
	Mbr1			Deletion protects yeast against stress [59].

[a]The supernumerary proteins present in the last common eukaryotic ancestor are shaded in gray [70,71,72,73,74,75].

with the nitric oxide associated-1 (NOA1) GTPase required for protein synthesis and Complex I [29,30], suggesting that this ribosomal protein may be involved in ribosomal docking to the mitochondrial inner membrane. Crosslinking of IF3mt to mitochondrial ribosomes has shown that MRPS29 may be in close proximity to three other supernumerary small subunit ribosomal proteins, MRPS36, MRPS32 and PTCD3 (discussed below) [2]. MRPS29 was initially identified as death-associated protein 3 (DAP3) because of its role in apoptosis [31], similarly to MRPS30 that was identified as programmed cell death 9 (PDCD9) protein because of its homology to the chicken pro-apoptotic protein p52 [32]. Interestingly, knockout of the yeast ortholog of DAP3, Rsm23, leads to mitochondrial dysfunction and loss of mtDNA [31]. Loss of mtDNA caused by deficiency or mutations in mitochondrial ribosomal proteins is commonly found in yeast [33]. The subsequent identification of both DAP3 and PDCD9 as MRPS29 and MRPS30 respectively [34], has stimulated the notion that perhaps these two proteins may have a dual role in protein synthesis and regulation of apoptosis [34]. However it is not clear if their role in apoptosis is a consequence of disrupted mitochondrial protein synthesis.

Recently, we found that the supernumerary proteins MRPS27 and PTCD3 belong to the pentatricopeptide repeat (PPR) domain family of RNA-binding proteins [35] and both are essential for protein synthesis [36,37]. It has been shown that PTCD3 associates with the 12S rRNA and is a component of the small subunit of mitochondrial ribosomes [2,37]. Although PTCD3 has been found crosslinked to IF3mt its location within the mitochondrial ribosome is not clear, however it is thought that it may be located at the interface side of the 28S subunit because of its association with other supernumerary proteins (MRPS29, MRPS32 and MRPS36) [2]. The other ribosomal PPR protein, MRPS27, also associates with the small subunit of the mitochondrial ribosome [36] as predicted by bioinformatic approaches and high throughput proteomics [29,31], and although it associates with the 12S rRNA, it is not involved in the regulation of its abundance. Instead, MRPS27, like PTCD3, is required for the translation of all 13 polypeptides [36]. Both PTCD3 and MRPS27 have been found associated with other ribosomal proteins or with ribosomal factors. For example, MRPS27 associates with the immature colon carcinoma transcript-1 (ICT1) mitochondrial translation factor [38] and the mitochondrial ribosome assembly factor Era G-protein-like 1 (ERAL1) [39], which are part of or associated with the large ribosomal subunit. PTCD3 has been found associated with POLRMT and a putative DEAD-box RNA helicase, DHX30, within the mitochondrial nucleoid [40], providing some evidence to the notion that transcription and translation may be coupled or at least that the mitochondrial nucleoid is in close proximity to mitochondrial ribosomes at the inner membrane. The role of MRPS33 in the mitochondrial ribosome is not clear but it has been shown that this supernumerary protein is important for cell function as MRPS33 gene haploinsufficiency in *Drosophila melanogaster* can cause cardiomyopathy [41].

Yeast mitochondrial mRNAs have long untranslated regions (UTRs) at the 5′ and 3′ ends that are important for binding of specific translation activation factors that regulate protein synthesis and the stability of individual mRNAs [42,43]. The translational activator of cytochrome *c* oxidase subunit 1 (TACO1) is the only mRNA specific regulator of translation identified in animal mitochondria to date [44], however, in yeast mitochondria there are a number of different translational activators of specific mRNAs [42,43]. Four of the 11 yeast-specific supernumerary proteins within the small mitochondrial ribosomal subunit associate with these specific translational activators and play a role in the recognition and translation of particular mRNAs. For example, the yeast-specific supernumerary protein of the small ribosomal subunit Mrp51 is required for global mitochondrial translation. Mutations in MRP51 can suppress defects in the 5′ UTR of COX2 and COX3 mRNAs, however they are not sufficient to by-pass the specific translation activation system [45]. Mrp1 and Pet123 are other examples of yeast-specific supernumerary proteins that interact with Pet122, a COX3 translational activator, to specifically promote translation of this

mRNA [46]. The supernumerary Rsm28 protein in yeast is not essential for mitochondrial protein translation, but it is required for the expression of COX1, COX2 and COX3 mRNAs in yeast mitochondria [47]. Rsm28 has been found to interact with initiation factor 2 (IF2mt) and the methionyl-tRNA-formyltransferase suggesting that it may have a role in translation initiation in yeast [47]. The role of the other yeast specific supernumerary proteins within the ribosome remains to be determined. Clearly both yeast and mammalian supernumerary proteins have defined roles within the small ribosomal subunit that either reflect the different structure of the mitochondrial transcripts in these systems or are a result of different pressures that have been exerted on the mechanisms of decoding in these systems following their divergence.

3.2. Supernumerary proteins of the large ribosomal subunit

The mitochondrial large ribosomal subunit is responsible for peptide bond formation, peptide chain elongation and facilitating the early stages of protein folding [48]. In mammals this subunit is composed of 49 proteins, of these 28 are core ribosomal proteins that share homology with prokaryotic ribosomal proteins and 21 are supernumerary proteins (Table 2). Little is known about the role of MRPL41 within the large ribosomal subunit beyond the fact that it may be located in close proximity to the polypeptide exit channel along with MRPL44 and MRPL45 based on experiments done with the yeast homologs of these proteins Mrpl27, Mrpl3 and Mba1 [5,49]. However, MRPL41 is suggested to have a pro-apoptotic role by binding to Bcl-2 before it is imported inside the mitochondrial matrix [50]. It would be curious to identify the mechanism by which a pre-processed MRPL41 induces apoptosis in cells. The yeast homolog of MRPL44, Mba1, has been located at the exit channel of the mitochondrial ribosome where it functions as a ribosome receptor that associates with the inner mitochondrial membrane protein Oxa1 to position the ribosome exit site at the inner membrane [5,49]. This has not been shown in animals yet, although mitochondrial ribosomes have been found associated with the inner mitochondrial membrane [51]. Furthermore, crosslinking of the large ribosomal subunit to the mammalian inner membrane protein Oxa1 L, required for insertion of nascent polypeptides from mitochondrial ribosomes into the inner membrane, has identified its association with supernumerary proteins MRPL48, 49 and 51 in addition to those homologous to bacterial ribosomal proteins MRPL13, 20 and 28. Interestingly, one of the core ribosomal proteins, Mrpl32 (a homolog of the bacterial rpl32 protein), was found to tightly associate with the inner membrane following its processing by the m-AAA protease [52]. This indicates that Mrpl32 may mediate the association of mitochondrial ribosomes with the inner membrane.

MRPL55 has been studied in *Drosophila* where it was found to be essential for mitochondrial biogenesis and the progression from G2 to M phase of the cell cycle [53]. This protein shares the KOW-like motif found in RNA-binding proteins involved in transcriptional antitermination and regulation of translation [53], however its role within the mitochondrial ribosome is not clear. Recently, two additional proteins have been identified as supernumerary proteins of the large subunit. C7orf30, has been found associated with the large ribosomal subunit and is required for its stability and consequently mitochondrial translation and respiratory function [54,55]. The ICT1 protein, that has homology with class 1 release factors, was found when the protein responsible for termination of mitochondrial translation, mitochondrial release factor 1a, was used as bait in immunoprecipitation experiments [38,56,57]. ICT1 was found to be a ribosome dependent peptidyl-tRNA hydrolase that is not codon specific and is part of the mitochondrial large subunit. ICT1 may have a role in the hydrolysis of prematurely terminated peptidyl-tRNAs and thereby in recycling of stalled mitochondrial ribosomes [38].

There are six yeast-specific supernumerary proteins of the large mitochondrial subunit and very little is known about their role in the ribosome. Mrpl13 has been found in close proximity to the exit channel of the mitochondrial ribosome [49]. Mrpl25 has reduced replicative aging and resistance to oxidative stress that seems to be independent of mitochondrial translation, suggesting that this protein may have two distinct roles in yeast mitochondria [58]. Although deletion of the *MBR1* gene confers resistance against stress in yeast [59], it is interesting to note that deletion of either the Mbr1 or Mrpl25 proteins does not yield a respiratory deficient phenotype, suggesting that they may be required to fine-tune specific aspects of mitochondrial gene expression in yeast.

3. Supernumerary mitochondrial ribosomal proteins in human disease

Significant insight into the regulation of mitochondrial gene expression has come from human diseases caused by mutations in genes encoding mitochondrial proteins that lead to mitochondrial dysfunction [60]. The role of MRPS22 in the small ribosomal subunit was identified when a mutation in its gene was found to impair assembly of the small ribosomal subunit and result in compromised OXPHOS activity causing edema, fatal cardiomyopathy and tubulopathy [61,62]. Mutation in the SPG7 gene that encodes paraplegin causes hereditary spastic paraplegia and impairs the processing of MRPL32. Incorrectly processed MRPL32, is not assembled into the mitochondrial ribosome leading to impaired mitochondrial protein synthesis [52].

Advances in next generation technologies have enabled the detailed investigation of genomes from mitochondrial disease patients and the identification of new mutations in mitochondrial genes. Recently whole exome sequencing has identified MRPL44 as a new disease gene causing mitochondrial infantile cardiomyopathy [63]. Decreased levels of MRPL44 as a result of an L156R mutation were shown to affect the assembly of the mitochondrial large ribosomal subunit and the stability of 16S rRNA [63]. Interestingly, mitochondrial protein synthesis was not severely impaired in fibroblasts [63], suggesting that there may be tissue-specific effects of mutations in mitochondrial proteins involved in translation, as has been observed before for mutations in aminoacyl-tRNA synthetases (aaRSs) that result in remarkable phenotypic heterogeneity [60]. Exome and whole genome sequencing hold great promise for the discovery of new mutations in other mitochondrial ribosomal genes including those encoding supernumerary proteins. This would enable researchers to gain insights into the importance and possible roles of these unique additions to the mitochondrial ribosome.

4. Conclusions

The distinct and diverse compositions of mitochondrial ribosomes illustrate the high evolutionary divergence found between mitochondrial genetic systems. Some of these supernumerary proteins have common roles or positions within mitochondria of higher and lower eurkaryotes, while others appear to be organism-specific. Elucidating the role of the organism-specific supernumerary proteins may provide a window into the regulation of mitochondrial gene expression through evolution in response to distinct evolutionary paths taken by mitochondria in different organisms.

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