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Review Article

Properties of Human Mitochondrial Ribosomes

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Summary

Mammalian mitochondrial ribosomes (55S) differ unexpectedly from bacterial (70S) and cytoplasmic ribosomes (80S), as well as other kinds of mitochondrial ribosomes. Typical of mammalian mitochondrial ribosomes, the bovine mitochondrial ribosome has been developed as a model system for the study of human mitochondrial ribosomes, to address several questions related to the structure, function, biosynthesis and evolution of these interesting ribosomes. Bovine mitochondrial ribosomal proteins (MRPs) from each subunit have been identified and characterized with respect to individuality and electrophoretic properties, amino acid sequence, topographic disposition, RNA binding properties, evolutionary relationships and reaction with affinity probes of ribosomal functional domains. Several distinctive properties of these ribosomes are being elucidated, including their antibiotic susceptibility and composition. Human mitochondrial ribosomes lack several of the major RNA stem structures of bacterial ribosomes but they contain a correspondingly higher protein content (as many as 80 proteins), suggesting a model where proteins have replaced RNA structural elements during the evolution of these ribosomes. Despite their lower RNA content they are physically larger than bacterial ribosomes, because of the 'extra' proteins they contain. The extra proteins in mitochondrial ribosomes are 'new' in the sense that they are not homologous to proteins in bacterial or cytoplasmic ribosomes. Some of the new proteins appear to be bifunctional. All of the mammalian MRPs are encoded in nuclear genes (a separate set from those encoding cytoplasmic ribosomal proteins) which are evolving more rapidly than those encoding cytoplasmic ribosomal proteins. The MRPs are imported into mitochondria where they assemble coordinately with mitochondrially transcribed rRNAs into ribosomes that are responsible for translating the 13 mRNAs for essential proteins of the oxidative phosphorylation system.

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Abbreviations: HGNC, Human Genome Nomenclature Committee; kDa, kiloDaltons; MRP,mitochondrial ribosomal protein; MRPLs, large subunit mitochondrial ribosomal proteins; MRPSs, small subunit mitochondrial ribosomal proteins; pI: isoelectric point; r-proteins, ribosomal proteins; rRNA, ribosomal RNA

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INTRODUCTION

The discovery of ribosomes in mitochondria (*1, 2*) foreshadowed the surprising diversity of ribosome types in nature. The prevailing notion was that ribosomes occur in two forms, a smaller, 70S variety in prokaryotes and a larger, 80S kind in eukaryotes. It was expected that organellar ribosomes would be 70S particles, reminiscent of their ancestral prokaryotic origins. However, human (mammalian) mitochondria contain 55S ribosomes (*3*). These ribosomes resemble bacterial ribosomes and eukaryotic cytoplasmic ribosomes in their main functional properties, but in terms of their fine structure and physical-chemical properties, they differ unexpectedly from both these kinds of ribosomes, as well as from other kinds of mitochondrial ribosomes (*4*).

Having about the same mass as bacterial ribosomes, they contain scarcely half as much rRNA and over twice as much protein, differences which markedly affect their sedimentation coefficient and buoyant density. Many of the MRPs are distinctive, having no closely related homologues in bacterial or eukaryotic-cytoplasmic ribosomes and they are evolving rapidly. Also, human mitochondrial ribosomes have acquired an intrinsic GTP binding protein in the small subunit, an unprecedented occurrence in translational systems (*5*). The unusual properties of these ribosomes raise questions about their relation to other kinds of ribosomes. Their large number of proteins raises questions about their functional and structural organization, and also about the identity of individual MRPs that are homologous to proteins in other ribosomes. The bovine mitochondrial ribosome has been developed as a model system for mammalian mitochondrial ribosomes (*6*) to address several questions related to the structure, function, biosynthesis and evolution of these interesting ribosomes.

PROPERTIES OF HUMAN MITOCHONDRIAL RIBOSOMES

Sedimentation coefficient

The physical-chemical properties of mitochondrial ribosomes from different mammals are remarkably similar. A low

rRNA content, compensated by a higher protein content, results in a low buoyant density for these ribosomes, and a correspondingly slower sedimentation rate (*7*). The 55S ribosome has a sedimentation coefficient of 55–56S in different mammals and the small and large subribosomal particles have sedimentation coefficients of 28S and 39S, respectively (*3, 8*).

Size

Despite their low RNA content and lower sedimentation coefficient, 55S ribosomes are actually *larger* than 70S bacterial (*E. coli*) ribosomes, both on the basis of particle mass, and physical dimensions. Bovine 55S mitoribosomes have a mass of 2.83×10^6 Da (*7*) and rat 55S mitoribosomes are reported to have a mass of 3.57×10^6 Da (*8*). The latter figure probably represents an overestimate, since the calculations to arrive at this figure incorporated larger values for the protein content than appears to be contained in mammalian mitochondrial ribosomes (*9*, and Tables 1 and 2). Indeed, the 55S ribosome mass calculated from the known RNA (section 3.1) and protein components (section 3.2) is 2.64×10^6 Da. Furthermore, values for the mass of the 28S subunit, 1.01×10^6 Da, and that of the 39S subunit, 1.63×10^6 Da, are close to the earlier estimates (*9*).

The 55S ribosomes are intermediate in size between bacterial and cytoplasmic ribosomes when analyzed by pore-gradient acrylamide gel electrophoresis (*12*). This size difference is also apparent by electron microscopy. The dimensions of negatively stained rat 55S ribosomes (26.2 nm, long axis) are 24% larger than 70S *E. coli* ribosomes (21 nm, long axis) (*8*).

COMPOSITION OF MAMMALIAN MITOCHONDRIAL RIBOSOMES

Ribosomal RNAs

Mammalian mitochondrial ribosomes contain smaller RNAs than do bacterial ribosomes and they also lack the 5S component found in most other ribosomes. The 12S RNA in the small subunit of human mitochondrial ribosomes is only 954 nucleotides long (323 kDa). As such, it is about 40% shorter than bacterial 16S RNA. The 16S RNA in the large subunit of human mitochondrial ribosomes is only 1558 nucleotides long (528 kDa), only about half as large as bacterial 23S RNA (*13*). These mitochondrial rRNAs contain fewer modified nucleotides than other kinds of rRNAs. The few methylated nucleotides they do contain appear to be concentrated on the subunit interfacial regions (*14*). While the large subunit RNAs of bacteria contain four to eight pseudouridines, and those of mammalian cytoplasmic ribosomes contain as many as 57 pseudouridines, the corresponding mitochondrial RNA contains only a single pseudouridine at a conserved site within the peptidyl transferase domain (*15*). The conservation of this single pseudouridine in an otherwise highly divergent rRNA argues strongly for the functional importance of this modification.

Ribosomal proteins

Estimates for the number of proteins in mammalian mitochondrial ribosomes have ranged from about 85 (*9*) to more than 100. Recently, three different groups using proteomic approaches to analyze the proteins of bovine mitochondrial ribosomes (*16–27*) have obtained sequence information for virtually all of the MRPs (about 80) (Tables 1 and 2). Yeast MRPs are also available, for comparative purposes (*28, 29*). The nomenclature system originally used to identify bovine MRPs was based on their electrophoretic properties (*9*). Now that amino acid sequence information is available for these proteins, it is possible to identify homologues of bacterial ribosomal proteins, and the nomenclature being adopted by the Human Genome Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature/genefamily/MRPs.html) for the MRPs now reflects such homology. In this nomenclature designation, MRP homologues of bacterial proteins are assigned the same number (MRPS1 through MRPS21, for example). MRPs for which bacterial homologues do not exist are assigned higher numbers.

The amino acid sequence is known for 30 proteins in the small subunit (Table 1), including three isoforms of MRPS18 (*21*). The three S18 isoforms differ remarkably in sequence and size, ranging from 11.7–27 kDa. Each has a variation of a 'core' sequence showing homology to that portion of bacterial S18 involved in binding to the rRNA. The implication of this finding is that human mitochondrial ribosomes are heterogeneous, depending on which isoform they contain, and raises the possibility of functional specialization for the different mitochondrial ribosomes. With any one of the S18 isoforms the small subunits contain 28 different proteins, seven more than are present in the small subunits of eubacterial ribosomes. As expected, most of the bacterial ribosomal proteins have counterparts in the human mitochondrial ribosome (Tables 1 and 2). However, homologues for the small subunit proteins S1, S3, S4, S8, S13, S19 and S20 have not been found (*21*). These are either absent from mitochondrial ribosomes, replaced by other proteins, or are so highly divergent that they cannot be identified with confidence. In this regard, some of the mammalian MRPs having no identifiable homologue in bacterial ribosomes, MRPS22 through MRPS36, may replace the 'missing' proteins.

The amino acid sequence is known for 48 proteins in the large subunit (Table 2), thus bringing the total number of proteins in human mitochondrial ribosomes to 78. Mitochondrial homologues have been identified for all of the bacterial large subunit proteins except for L5, L6, L25, L29 and L31. Lacking L5 and L25, proteins binding to the 5S RNA of bacterial ribosomes, is consistent with the absence

Table 1
Molecular weights and isoelectric points of small subunit proteins* from human mitochondrial ribosomes, compared to *E. coli* ribosomal proteins

E. coli small subunit			Human MRPSs			
Protein	mass(kDa)	pI	Protein	mass(kDa)	pI	Yeast MRP?
S1	61	4.8				
S2	26.7	7.1	MRPS2	30.1	9.1	MRP4p
S3	26	10.9				Var1p
S4	23.4	10.6				NAM9p
S5	17.6	10.8	MRPS5	38.8	10.6	MRPS5
S6	15.1	5.3	MRPS6	13.8	9.5	MRP17
S7	20	10.9	MRPS7	24.3	9.6	Rsm7p
S8	14	10.1				YMR158w
S9	14.8	11.3	MRPS9	40.5	9.9	MRPS9
S10	11.7	10.3	MRPS10	17.7	6.2	S59279
S11	13.8	11.5	MRPS11	20	11.1	MRPS18
S12	13.7	11.3	MRPS12	12.8	10.9	P53732
S13	13.1	11.2				Pet123p
S14	11.5	11.4	MRPS14	13.2	11.5	MRP2
S15	10.2	10.9	MRPS15	27.9	10.9	MRPS28
S16	9.2	11	MRPS16	14.3	10.2	YPL013C
S17	9.7	10.3	MRPS17	12.9	10.3	YMR188C
			MRPS18A	18.8	10.9	
			MRPS18B	27	9.9	
S18	8.9	11	MRPS18C	11.7	10.2	YER050C
S19	10.4	11.2				YNR037c
S20	9.6	11.6				
S21	8.5	11.4	MRPS21	10.5	10.7	YBL090W
			MRPS22	35.3	6.4	
			MRPS23	21.2	9	YIL093C
			MRPS24	15.3	9.9	
			MRPS25	20	9.4	YKL167C
			MRPS26	21.3	10.2	
			MRPS27	44.6	5.4	
			MRPS28	13.1	8.2	
			MRPS29	43.1	9	YGL129C
			MRPS30	47.7	7.3	
			MRPS31	39.4	10	
			MRPS33	9.7	10.8	Rsm27p
			MRPS34	25.7	10.6	
			MRPS35	34.6	8	YDR175C
			MRPS36	10.2	10.2	YMR-31

*HGNC nomenclature.
Mass value listed for the MRPs are for the mature protein, determined by N-terminal sequence analysis, or predicted by TargetP (*10*) and MitoProt (*11*).

of 5S RNA in human mitochondrial ribosomes. Some of the 'extra' proteins, MRPL37 through MRPL56, for which no bacterial homologues exist, may replace some of the missing proteins.

The mammalian mitochondrial ribosome is indeed protein rich, with the large subunit containing 48 identified proteins, 15 more than are present in the large subunit of bacterial (*E. coli*) ribosomes. We now see that, despite the loss of half of their RNA, and losing a protein mass of 223 kDa, human mitochondrial ribosomes have nevertheless grown *larger* than bacterial ribosomes, by acquiring 34 extra proteins of aggregate mass 873 kDa (Tables 1 and 2).

Table 2
Molecular weights and isoelectric points of large subunit proteins* from human mitochondrial ribosomes, compared to *E. coli* ribosomal proteins

E. coli large subunit			Human MRPLs			
Protein	mass (kDa)	pI	Protein	mass (kDa)	pI	Yeast MRP?
L1	24.7	10.3	MRPL1	32	7.3	CAA88669
L2	29.9	11.3	MRPL2	28.2	11.5	Yel050cp
L3	22.2	10.6	MRPL3	34.4	9.9	YmL9
L4	22	10.4	MRPL4	33	9.9	CAA86630
L5	20.3	10.1				YmL5
L6	18.9	10.3				
L9	15.8	6.5	MRPL9	24.8	10.1	
L10	17.7	9.6	MRPL10	26.4	9.6	YmL11
L11	14.9	10.3	MRPL11	16.3	9.8	YmL19
L12	12.3	4.56	MRPL12	16.5	5.3	YGL068W
L13	16	10.5	MRPL13	19	9.4	YmL23
L14	13.5	11	MRPL14	12.6	11	YmL38
L15	15	11.5	MRPL15	31.3	10.5	YmL10
L16	15.3	11.5	MRPL16	25.3	10.1	YmL47
L17	14.4	11.3	MRPL17	19.4	10.5	YmL8
L18	12.8	11	MRPL18	18	9.6	
L19	13.1	11.1	MRPL19	29	10	Img1p
L20	13.5	11.6	MRPL20	16.4	11.2	
L21	11.6	10.5	MRPL21	18.9	10.2	MRPL49
L22	12.2	10.9	MRPL22	19.4	10.4	Yml177cp
L23	11.2	10.7	MRPL23	14.1	8.5	YmL41
L24	11.3	11	MRPL24	23.9	9.7	CAA97022
L25	10.7	10.2				
L27	9.1	11.2	MRPL27	13	10.4	YmL2
L28	9	11.6	MRPL28	27	8.3	YmL24p
L29	7.3	10.7				
L30	6.5	11.3	MRPL30	14.7	10.7	YmL33
L31	7.9	10				
L32	6.4	11.4	MRPL32	12.8	9.8	YmL32
L33	6.4	10.9	MRPL33	6.7	10.8	YmL39
L34	5.4	13	MRPL34	5.4	12.3	CAA88667
L35	7.3	12	MRPL35	21.5^{P}	11.6	YCR018C
L36	4.4	11.3	MRPL36	4.9	11.2	CAA97895
			MRPL37	45.3	8.8	
			MRPL38	41.2	9.3	YmL35
			MRPL39	36.6	7.5	
			MRPL40	19.3	10	
			MRPL41	14	10	YmL27
			MRPL42	13.1	7.2	
			MRPL43	20.7	9.6	Ypr100wp
			MRPL44	34.4	7.3	MRPL3p
			MRPL45	33.7	9.6	
			MRPL46	28.2	5.6	MRPL17p
			MRPL47	28.2	10.9	MRPL4
			MRPL48	20.6	8.2	
			MRPL49	16.4	7.4	NP_009996

(continued overleaf)

Table 2
(continued)

E. coli large subunit			Human MRPLs			
Protein	mass (kDa)	pI	Protein	mass (kDa)	pI	Yeast MRP?
			MRPL50	17.8	7.3	
			MRPL51	11.7	11.4	RSM10
			MRPL52	11.3	7.4	
			MRPL53	12.1[P]	9.4	
			MRPL54	14.3	9.7	MRPL37p
			MRPL55	11.6	10.7	
			MRPL56	58.8	8.7	

*HGNC nomenclature; mass for MRPL35 and MRPL53 is that of the precursor ([P]) proteins.
Mass value listed for the MRPs are for the mature protein, determined by N-terminal sequence analysis, or predicted by TargetP (*10*) and MitoProt (*11*).

EVOLUTION OF MRPS

Origin of MRPs

Mitochondria appear to have arisen from an early endosymbiosis between a eubacterium and the host cell (*30*). Members of the rickettsial subdivision of the alpha-Proteobacteria are considered to be among the closest known eubacterial relatives of mitochondria. Like *E. coli*, these bacteria contain 70S ribosomes and their RNA and protein composition is very similar to that of *E. coli* ribosomes. The ancestral endosymbiont probably had 70S ribosomes of similar composition. Mitochondrial ribosomes have undergone some major remodeling during their intracellular evolution, losing RNA and adding proteins, in the case of human mitochondria. Not unexpectedly, most of the human MRPs that have bacterial homologues also have homologues in yeast mitochondrial ribosomes (Tables 1 and 2), reminiscent of their common, eubacterial origin. Not so, however, for the 'new' MRPs that do not have homologues in bacteria. Fewer of the MRPs in this category have homologues in yeast mitochondria, suggesting that these MRPs were acquired in response to different molecular events, such as loss of rRNA structural elements, in the human line, but not in fungi, a consequence of their divergent intracellular evolution. It is noteworthy, however, that humans and fungi do have a few similar MRPs in this category, probably reflecting an earlier, common evolutionary history for these endosymbionts.

Rapid evolution of mammalian MRPs

The proteins in mammalian mitochondrial ribosomes are evolving more rapidly than those from cytoplasmic ribosomes in the same cell. From a pairwise analysis of homologous proteins in bovine and rat mitochondrial ribosomes, as well as proteins in bovine and rat cytoribosomes (319) it was estimated that the mitoribosomal proteins are changing at a rate 13 times higher than for cytoplasmic ribosomal proteins. This rate, calculated for the entire complement of ribosomal proteins, corresponds to an average identity of about 80% between bovine and rat mitoribosomal proteins. Analysis of nucleotide substitution rates for mammalian mitoribosomal RNAs indicates that they are evolving at rates about 23 times that of the more conserved cytoplasmic rRNAs (*31*). The result that that the mitoribosomal RNA and proteins are changing at comparable rates is especially interesting in view of the fact that they are products of different genomes, where mutational rates are estimated to differ 3–10-fold. Comparison of the ribosomal protein and rRNA rates of evolution suggests that the changes are being fixed at comparable rates in both the RNA and protein components of mitochondrial ribosomes, despite the different mutational rates for the RNA and protein. This implies that functional constraints act more or less equally on both kinds of molecules in the ribosome. A similar relationship also holds for cytoplasmic ribosomes in which, despite their overall higher degree of conservation, the RNA and proteins show essentially the same evolutionary rate (*31*). Such concordant evolution of RNA and protein components in two kinds of ribosomes, which are evolving at different rates, implies that the proteins, as well as the RNA, are subjected to effectively similar structural/functional constraints.

RIBOSOME EVOLUTION WITH PROTEIN PROSTHESES

The two-fold greater quantity of total protein in mammalian mitochondrial ribosomes is due partially to a somewhat larger average size of the individual proteins and partially to the larger number of proteins (*9*; Tables 1 and 2). If the ancestral endosymbiont had 70S ribosomes of similar composition to those of eubacteria (section 4.1) how did the mammalian mitochondrial ribosome acquire the additional proteins? Was it by gene duplication, or was it by recruitment of new proteins? It now appears that both of these processes have been operating. Three isoforms exist for MRPS18 (*21*).

Apparently two rounds of duplication of the gene for mammalian MRPS18 occurred giving rise to three very different isoforms (Table 1); two of these are near each other on human chromosome 6, MRPS18A at the locus 6p21.1 and MRPS18B at 6p21.3, while the gene for MRPS18C is on chromosome 4 at 4q21.23.

Mammalian mitochondrial ribosomes lack several of the major RNA stem structures of bacterial ribosomes (*32*) but they contain a correspondingly higher protein content, suggesting a model where proteins have replaced RNA structural elements in these ribosomes (*33*). If loss of rRNA helices (through replication slippage? or unequal recombination?) in the endosymbiont did not otherwise interfere with ribosome assembly, the resulting particle is expected to have a cylindrical cavity in place of the missing stem. This cavity flanked by basic ribosomal proteins could recruit proteins, preferentially those with acidic domains mimicking RNA structure, from within the mitochondrial matrix (Fig. 1). Predictions of this model are consistent with known biochemical information: (1) the 'extra/new' ribosomal proteins are not homologues of proteins in bacterial, eukaryotic cytoplasmic or yeast mitochondrial ribosomes (which have not lost the corresponding RNA structures); (2) the new ribosomal proteins tend to have lower isoelectric points (Tables 1 and 2); (3) recruited proteins are pre-existing (bifunctional); and (4) protein-protein interactions predominate in mammalian mitochondrial ribosomes (*35*).

One striking example of the recruitment of a pre-existing protein is the acquisition of the protein MRPL39 (*36*). This protein, originally named MRP-L5 (*9, 17*), is similar to the N-terminal domain of a mitochondrial threonyl-tRNA synthetase. Conceivably, this protein was recruited to the ribosome in the form of mitochondrial threonyl-tRNA synthetase, later losing the central and C-terminal domains by adaptive

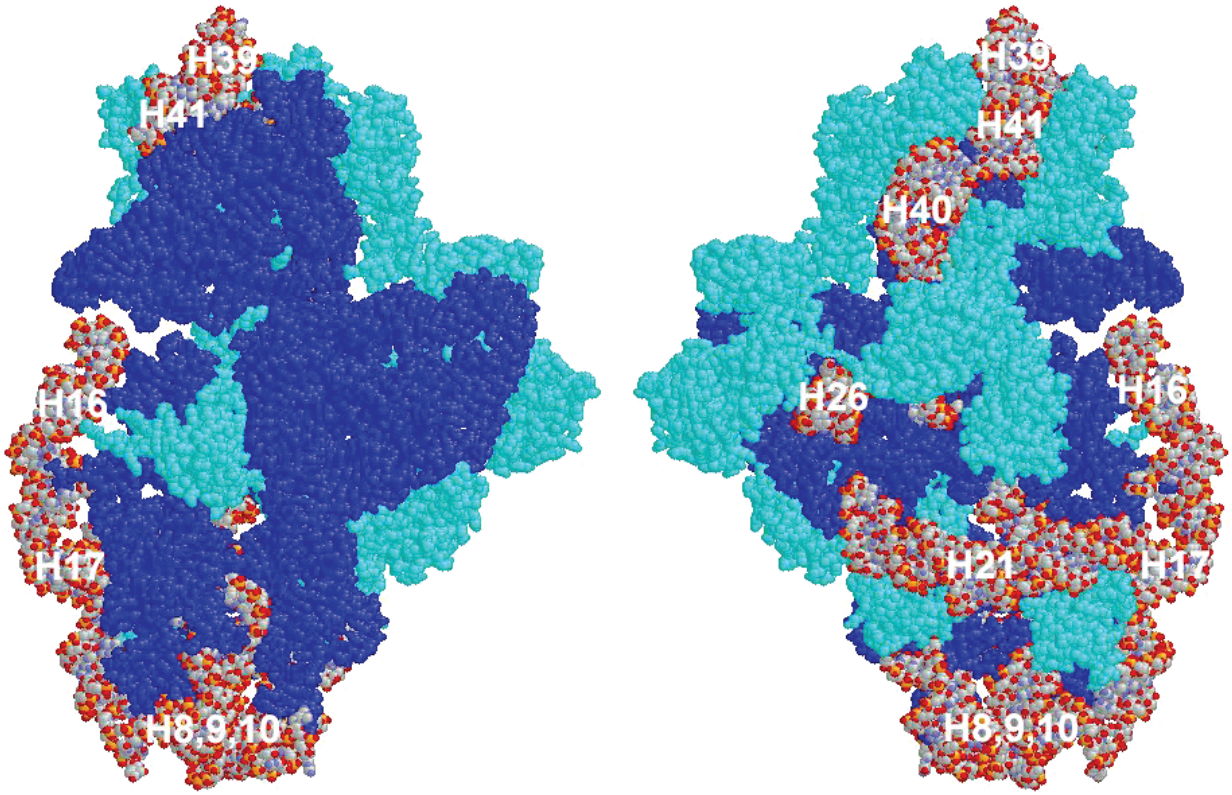

Figure 1. Structural model of the 28S small subunit of the human mitochondrial ribosome illustrating the location of RNA helices (in bacterial ribosomes) that are missing in the human ribosome. On the left is a view of the interfacial aspect of the small subunit (from the perspective of the large subunit) and on the right is a view of the opposite surface of the small subunit. The 12S RNA is blue, and proteins that are conserved between bacteria and human mitochondria are cyan colored. Missing helices (H), identified by their number, are rendered in CPK colors. Proteins flanking the missing helices are expected to recruit protein replacements. Locations of the individual 'extra' proteins (MRPs S22-S36) are presently unknown. Spatial coordinates for the RNA and conserved proteins are from (*34*).

evolution. Significantly, the tRNA binding site in the N-terminal domain is conserved in MRPL39 (*36*), but whether or not the ribosome has 'learned' to use this RNA binding site remains an open question.

Another mechanism for compensating the loss of RNA structures is for existing ribosomal proteins to become enlarged, acquiring N- or C-terminal extensions (*26, 27*). Several of the MRP homologues of bacterial r-proteins (Tables 1 and 2) have significantly larger mass. These extensions into sites originally occupied by RNA could help to stabilize the ribosome structure, restoring function to a ribosome crippled by loss of an RNA structural element. The recruitment of new proteins to replace lost RNA and the extension of ribosomal proteins into regions formerly occupied by RNA are graphic examples of the evolution of mammalian mitochondrial ribosomes from an 'RNA world' into a 'protein world', where proteins assume the function of RNAs. It should be interesting to accelerate this process experimentally, using a bacterial model of the mitochondrial ribosome, to observe the further recruitment of new proteins to the remodeled ribosome.

Why, in view of their many extra proteins, are mammalian mitochondrial ribosomes so different from bacterial ribosomes and those of chloroplasts and even plant and fungal mitochondria? The answer may lie in the fact that these other ribosomes did not suffer the RNA amputations obvious in the mammalian mitochondrial ribosome, probably because the corresponding deletions were corrected, as they occurred, by processes of gene conversion or recombination. Mammalian mitochondria, deficient in these activities, would retain the mutated rDNA, amidst a population of otherwise normal mitochondrial DNAs that could ensure a supply of functional ribosomes. Proteins recruited in place of the missing RNA could be remodeled during evolutionary time, restoring function to a crippled ribosome. Selective pressure to minimize the mitochondrial genome under these conditions may have favored the population expansion and segregation of the smaller mitochondrial genomes bearing the rDNA deletions.

RIBOSOME-RESIDENT GTP-BINDING PROTEIN

GTP binding site

The large number of proteins in mammalian mitochondrial ribosomes supports the idea that some of the extra proteins may be playing structural and/or functional roles served by RNA in the bacterial ribosome (section 5). Alternatively, some of the 'new' proteins in mitochondrial ribosomes may play a more significant role than a simple, 'space filling' role, as was suggested by the discovery of a novel GTP binding site on the small subunit of the bovine mitoribosome (*5*). GTP binds in unit stoichiometry and high affinity (K_d = 15 nM) to a site on the small subunit. The binding activity survives high salt washes, indicating that the nucleotide binds to an integral site within the subunit. The GTP binding can be competed by GDP, but not by other nucleotides, suggesting a direct functional role for GTP.

GTP binding protein

GTP photoaffinity analogues were used to identify the GTP binding protein as MRPS29 (MRP-S5 in the original nomenclature of (*9*)), one of the new proteins in mitochondrial ribosomes. The sequence of this mitoribosomal protein is identical to that of DAP3 ('death associated protein 3'), a protein implicated in apoptosis (*23, 37*). It appears that MRPS29 is a bifunctional protein. Whether the role of DAP3 in apoptosis is exerted from its position in the mitochondrial ribosome remains an open question. Perhaps the mitoribosome-based function of this GTP-binding protein is entirely separate from its role in apoptosis. On the other hand, a role for mitochondrial ribosomes in promoting apoptosis should not be overlooked, since another of the MRPs, MRPS30, has also been implicated in this process. MRPS30 and PDCD9 (programmed cell death protein 9) are the same protein (*23, 38*). Perhaps MRPS29 and MRPS30 cooperate in triggering a mitochondrially-induced apoptotic cascade.

GENES FOR MAMMALIAN MRPS

All of the 78 or more proteins in mammalian mitochondrial ribosomes are products of nuclear genes. These proteins are synthesized on cytoplasmic ribosomes (*39*) and must therefore be imported by mitochondria for assembly with the mitochondrially encoded rRNA. It appears that most, if not all, of the MRPs have cleavable, N-terminal extensions that serve as mitochondrial import signal peptides (*17, 24–27*). The MRP genes are scattered among the different chromosomes, with no hint that they were transferred en bloc, suggesting a piecemeal transfer over evolutionary periods, before the mitochondrial genetic coding changes occurred, blocking further transfers to the nucleocytoplasmic system.

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