Protein content of minimal and ancestral ribosome

ARCADY MUSHEGIAN

Stowers Institute for Medical Research, Kansas City, Missouri 64110, USA
Department of Microbiology, Molecular Genetics, and Immunology, University of Kansas Medical Center, Kansas City, Kansas 66160, USA

ABSTRACT

Minimal genome approaches seek to define the smallest gene complement compatible with modern-type cellular life on Earth. A consensus of computational and experimental approaches indicates that a minimal genome is close to 300 protein-coding genes, if a rich medium is provided for cell growth. I relate ribosomal gene content in completely sequenced genomes to ribosomal subunit structure and approximate the protein components of the putative minimal ribosome and the ribosome of the Last Universal Common Ancestor of Life. Both sets contain between 35 and 40 proteins. There is evidence of protein–protein and protein–RNA displacement in the evolution of both ribosomal subunits.

Keywords: ribosomal proteins; comparative genomics; gene displacement

INTRODUCTION

Reconstructions of a minimal genome (Koonin 2003) suggest that it would use about half of its gene products for simplified intermediate metabolism and the other half to control genome replication, repair, and gene expression. The latter category includes ribosomal proteins. Molecular functions of most of them remain poorly understood, whereas the two essential activities of the ribosome, decoding of mRNA and synthesis of peptide bonds, appear to be largely performed by the ribosomal RNA itself (Steitz and Moore 2003).

Ribosomal proteins exist in two main flavors—Bacterial, including endosymbiont-derived proteins of mitochondrial and chloroplast ribosomes, and Archaeo/Eukaryal. More specifically, if a ribosomal protein has orthologs in all living species, the sequence-based phylogenetic tree of such orthologs tends to display the ancient bifurcation of Bacteria (B) and Archaea/Eukarya (AE), followed by a more recent split of A and E. If a protein is not omnipresent, it is typically found either only in B or only in AE (Anantharaman et al. 2002; Lecompte et al. 2002; see Supplementary Material, available at <http://research.stowers-institute.org/bioinfo>, for a description of phylogenetic and other methods used in this work, as well as for additional discussion of the Tree of Life).

Mears et al. (2002) have defined minimal ribosomal RNA as the set of rRNA regions conserved in all living forms and two types of organelles. This minimal rRNA is approxi-

mated by two extremely deleted rRNAs found in mitochondria of nematodes. The small-subunit (SSU) rRNA in nematode mitochondria has lost ~55% of its nucleotides compared to an average bacterial homolog, the large-subunit (LSU) rRNA has lost 74%, and 5S RNA is missing in nematode mitochondria altogether. The remaining, universally conserved rRNA domains include most of the intersubunit interface, as well as the peptidyltransferase center and the sites of interaction with tRNAs.

rRNA from any species can be partitioned into three sequence components: regions that can be aligned to nematode mito-rRNA; those that do not align to mito-rRNA, but have a structural equivalent within it, for example, a non-conserved loop joining the halves of a conserved RNA hairpin; and sequences missing from nematode mito-rRNA. The first two components together can be viewed as minimal rRNA.

The protein component of minimal ribosome has been defined as the set of all ribosomal proteins present in three phyla and two organelles (3P2O in Mears et al. 2002). Here, I refine this set and derive the protein complement of the ancestral ribosome using a comparative-genomics approach.

RESULTS AND DISCUSSION

Minimal set of ribosomal proteins Min1: Recount of shared orthologs and their interactions with minimal rRNA

A lucky DNA sample is sufficient to detect gene presence in a given species. Gene absence, however, is definitive only when the entire genome sequence is available. Therefore,

Reprint requests to: Arcady Mushegian, Stowers Institute for Medical Research, 1000 E. 50th St., Kansas City, MO 64110, USA; e-mail: arm@stowers-institute.org; fax: (816) 926-2041.

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There are 32 ribosomal proteins with PPL1 (Fig. 2; see Supplementary Material, <http://research.stowers-institute.org/bioinfo>). To make the Min1 list, such a protein has to interact with Min rRNA. Although there is no high-resolution structure of any complete ribosome, the SSU structure from the bacterium *T. thermophilus* and LSU structures from the bacterium *Deinococcus radiodurans*

Minimal set Min2, which accounts for nonorthologous gene displacements

Any minimal set, if it includes only shared orthologs, underestimates the number of components, because one and the same function can be performed, in two species, by non-orthologous, and sometimes even nonhomologous, proteins (Koonin 2003). This is called nonorthologous gene displacement (Koonin et al. 1996), and in the case of the enzymes of intermediate metabolism, 5%–10% of genes may be so displaced (Galperin and Koonin 1999). Thus far, little is known about gene displacements among ribosomal proteins. One way to account for displacements is to compare phyletic patterns, looking for pairs of proteins found to the exclusion of one another. In the case of ribosomal proteins, the candidates are obvious: Many proteins are found either only in Bacteria (PPL3–4; Table 1) or in Archaea/Eukarya (PPL5–6).

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FIGURE 1. Reconstruction of Minimal and Ancestral sets of ribosomal proteins. Proteins are partitioned on the basis of their interaction with minimal RNA and presence of their orthologs in all species and organelles. Proteins that are “positive” on both counts are the Min1 set. Min2 is produced by supplementing Min1 with nonorthologous proteins found in complementary subsets of species, which interact with the homologous region of Min RNA (nonorthologous displacements). Anc is obtained by inferring the presence of ribosomal proteins in LUCA, using the phylogenetic tree and the phyletic pattern of each ribosomal protein. Cartoons of LSU at various stages of reconstruction are shown. Coordinate files for reconstructions of both subunits are available on request.

Conceivably, a protein in one such group may contain an isofunctional protein in the other.

Most ribosomal proteins have roles in properly orientating functional rRNA subdomains upon ribosome assembly and in targeting regulatory factors to specific sites on the ribosome (Klein et al. 2004). The site of specific interaction between a ribosomal protein and rRNA, therefore, can be taken as an indication of its function, and when the interaction sites of the two proteins are similar, their function may be similar too. In the case of the large subunit, one can directly identify the cases when bacterial and archaeal ribosomal proteins interact with the homologous regions on Min rRNA. Analysis of LSUs from *H. marismortui* and *D. radiodurans* identifies probable displacements at six distinct locations within the large subunit, involving nine bacterial and eight archaeal proteins.

At the exit from the peptide tunnel, archaeal protein L31E and bacterial L17 are found at the same site. This region interacts with translocon as secreted peptides are inserted into the signal recognition particle. It would be interesting to know whether the differences in this process in bacteria and archaea have to do with different L17/L31E specificities. *Inside the exit tunnel*, two pairs of proteins are displacing each other. Elongated L39E displaces the nonglobular tail of bacterial L23, and L37E displaces bacterial L34. In the bacterial *peptidyltransferase center*, L27 interacts with P-loop and

tRNA. Archaeal L21E occupies a very similar position. *At the E site*, bacteria-specific L31 and L33 make contacts with helix 75 and tRNA, whereas in archaea this role is played by archaeo-eukaryal L15E and L44E. *At the intersubunit interface*, L19 is replaced by archaeal L24E. Both proteins are thought to form bridge B6 with the SSU, where they both interact with the Min1/Min2 member S14. At the Min domain of *helix 25*, the joint nonglobular regions of bacterial L20 and L21 play the same role as the nonglobular part of archaeo-eukaryal L32E. These displacements are discussed in more detail in Table 2; most of them have been noticed before (Harms et al. 2001; Klein et al. 2004). After these displacement cases are added to Min1, most protein–protein interactions in the large subunit are recovered, indicating that Min2 is functionally more coherent than Min1.

Anc, the ancestral set of ribosomal proteins

There is no requirement for LUCA to possess a minimal genome. Therefore,

to proceed from the Min2 to Anc set, we have to add the Min–Anc+ proteins to Min2, and to remove Min+Anc– proteins. Anc ribosome is allowed to gain some rRNA in the regions that interact with Min–Anc+ proteins. One way to find the Anc+ proteins is by using phyletic patterns together with the phylogeny of the protein sequences. There are two main possibilities: Either the pattern is found in every species (PPL1/PPL2 can be combined here, because the origin of organelles clearly postdates the LUCA) or it is not (PPL3–7).

A PPL1/2 gene is scored as ancestral if there is a good agreement between the phylogenetic tree of this gene and the Tree of Life (Mirkin et al. 2003; Supplementary Material, available at <http://research.stowers-institute.org/bioinfo>). The agreement of the two trees—as a first approximation, the same branching order on the protein family tree and the consensus species tree—suggests that the common ancestor of a given gene was present in LUCA, and the gene must have been acquired by the observed species mostly by vertical inheritance. If, however, there is significant difference between the topologies of the species’ tree and the gene tree, or if gene is missing in too many species, the ancestral state of the affairs is obscured. To reconcile the trees and to infer the status of such a gene in the common ancestor, one has to account for lineage-specific gene gains and losses and horizontal transfers (Arvestad et al. 2003; Mirkin et al. 2003). I tested the

	PDB chain	Protein complex	PPL	3P	3P2O	Min rRNA interactions	Min1	Min2	Anc / LUCA	NCBI COG
S2	b	bdehq	1							0052
S3	c	cijmns	1							0092
S4	d	bdehq	1							0522
S5	e	bdehq	1							0098
S6	f	fgkr	3					?	?	0360
S7	g	fgkr	1							0049
S8	h	bdehq	1							0096
S9	i	cijmns	1							0103
S10	j	cijmns	1							0051
S11	k	fgkr	1							0100
S12	l		1							0048
S13	m	cijmns	1							0099
S14	n	cijmns	2							0199
S15	o		2							0184
S16	p		3					?	?	0228
S17	q	bdehq	1							0186
S18	r	fgkr	3					?	?	0238
S19	s	cijmns	1							0185
L1			1							0081
L2/L8	a	a(z)	1							0090
L3	b	bejk(u)	2							0087
L4	c	cz	2							0088
L6	e	bejk(u)	2							0097
L7E	f	fm3	7							1841
L10	g		2							0244
L10E/L16	h		1							0197
L11	i		1							0080
L13	j	bejk(u)	2							0102
L14	k	bejk(u)	2							0093
L15	l		2							0200
L15E	m	fm3	5					L31/L33	?	1632
L21E	q	(dn)q	5					L27	?	2139
L22	r		1							0091
L23	s		1							0089
L24E	u		5					L19	?	2075
L24P	t		1							0198
L31E	x		5					L17	?	2097
L32E	y		5					L20/L21	?	1717
L37E	z	cz	5					L23/L34	?	2126
L39E	1		5					L23/L34	?	2167
L44E	3	fm3	5					L31/L33	?	1631

FIGURE 2. Protein content of Min1, Min2, and Anc. The chain identifiers for each molecule in the PDB file (1FJG for *Thermus* small ribosomal subunit and 1S72 for *Haloarcula* large subunit) are shown in the second column. Groups of proteins linked by protein-protein interactions are shown in the third column. Gray shading indicates that a protein belongs to the set shown at the top of the column, and a blank cell indicates that this protein is not a member of this set. Red cells indicate possible gene displacements, marked by question marks in the case of a small subunit and annotated in the case of a large subunit (cf. Table 2). The blue cell is a special case of S8 (see text). Yellow cells are proteins that join the Anc set because they have PPL1 and a compatible phylogenetic tree, and the green cell is L7E (PPL7), added to the Anc set by maximum-likelihood analysis of its phyletic pattern. The question marks in the Anc/LUCA column indicate that it is not known which version of this component (Bacterial, Archaeal/Eukaryal, or maybe RNA) was present in the LUCA.

ancestral hypothesis for all proteins with PPL1–2, and three of them, all in the LSU, showed the same topology as the consensus species' tree. These three proteins, L1, L23, and L24P, join the Anc set.

Given an explicit model of gene gains and losses, the compatibility of any "patchy" phyletic pattern and gene presence in LUCA can be quantitatively assessed (Mirkin et al. 2003; Supplementary Material, available at <http://research.stowers-institute.org/bioinfo>). I examined the phyletic patterns PPL3–7, and for one PPL7 protein, L07E, the hypothesis of its presence in LUCA was better supported than the alternative.

Several PPL1 proteins have unusual phylogenies: S14 in bacteria has undergone horizontal transfers and takeovers of gene function by a phylogenetically distant ortholog (Brochier et al. 2000), and two proteins, S15 and L01, branch unexpectedly deeply in *Treponema* and *Chlamydia*, respectively. All this overprinting, however, appears to have occurred within Bacteria, i.e., post-LUCA, and these proteins remain in the Anc set.

Direct analysis of gene displacements cannot be done for SSU because the structure is available only for a bacterial representative. However, three bacteria-specific proteins with PPL3, namely, S6, S16, and S18, contact Min-rRNA and may be displaced in archaea. In particular, S6 and S18 are part of the T4 RNP complex, which also includes Min and Anc protein S15 and helices 20 and 23 from Min-rRNA (Agalarov et al. 2000). S16, thought to play an auxiliary role in the assembly of that complex, interacts with the conserved end of helix 15. In archaeal SSU, there are seven AE/PPL5 proteins, not mapped to specific locations in a ribosome yet. Further studies of these proteins will test the prediction that some of them are displacing bacterial S6, S16, and S18 in archaeal/eukaryotic ribosome. I tentatively add S6, S16, and S18 to Min2 and Anc.

In *Thermus* SSU, a tiny, poorly structured THX protein interacts with several conserved regions of rRNA Domain III. A database search using the PSI-BLAST program (Altschul et al. 1997) suggests that THX is orthologous to ribosomal protein S31, known from chloroplasts and two plant-associated bacteria, *Xylella* and *Xanthomonas* (A. Mushegian, unpubl. observations). It is possible that counterparts of THX are found outside of this handful of genomes, but have not been recognized because of their small size or low sequence identity. Alternatively, they may be displaced by other proteins.

A more radical proposition is that some nonorthologous displacements may involve a protein and an RNA, i.e., the function of a deleted rRNA element is taken over by an extra protein or an insertion of additional nucleotides in rRNA obviates a need for a ribosomal protein. The most relevant observation here concerns the interactions between proteins and a nonminimal region of the LSU RNA. In the alignment of *Haloarcula* and *Deinococcus* RNA, there is a single long (50 bases) insert, which forms an extra length in RNA helix 25 in *Haloarcula*. This region of rRNA interacts with the globular domain of archaeal L32E protein. In bacteria, L32E is displaced by L20 and L21 (Klein et al. 2004; Table 2), but the RNA site that interacts with the L32E globular domain in archaea is not found in bacteria. Interestingly, however, bacterial L20 makes extensive contacts with the globular portion of L21, which, in turn, contacts L15 (PDB entry 1NKW). Thus, the archaea-specific extension of RNA helix 25 and the globular domain of bacteria-specific L21 may be isofunctional, yet they are obviously nonorthologous.

Another suggestion of an RNA-protein displacement comes from the unique case of protein S8. It interacts with SSU RNA

TABLE 2. Nonorthologous displacements of ribosomal proteins

Ribosome functional site	Bacterial protein (PDB ID 1NKW)	Fold class ^a	Archaeo/Eukaryal protein (PDB ID 1S72)	Fold class ^a	Comments
Exit tunnel opening	L17 (L)	4	L31E (W)	4	These proteins are from the different superfamilies of the broad $\alpha + \beta$ fold class, and have no sequence similarity.
Exit tunnel interior	L23 (R)	3–4	L39E (1)	1	See main text.
	L34 (2)	1	L37E (Z)	2	
Helix 25 (common part)	L20 (O)	1	L32E (X)	3	A 45-amino-acid loop in the middle of L32E protein penetrates the ribosome body, interacts with the min-rRNA region of helix 25, and makes some of the same RNA contacts as the extended regions of two proteins, L20 and L21, in bacteria. Typical of ribosomal proteins, L32E and L21 have many positively charged residues in these regions, but there is no clear indication of an evolutionary relationship.
	L21 (P)	2		3	
P-loop, P-tRNA	L27 (U)	2	L21E (P)	2	The same fold class, and some shared features, such as the strongly twisted β -sheet, but no specific sequence similarity between L27 and L21E.
Helix 75, E-tRNA	L31 (Y)	3	L15E (L)	4	The α - β region of L15E interacts only with non-Min rRNA and is not considered further. Elongated regions of L15E and L44E contact each other, helix 75, and E-tRNA. This composite protein structure is replaced by a single protein, L31, in bacteria. The globular part of L44E also interacts with E-tRNA, and is replaced by a globular protein L33 in bacteria. The folds of L33 and L44E are similar, and there is significant sequence similarity between L33 and L44E, covering most of the length of the shorter L33. The order of related sequence segments, however, is swapped. Thus, L33 and the globular part of L44E may be orthologs in disguise (Klein et al. 2004), properly belonging in Min1/Min2.
	L33 (1)	2	L44E (2)	2	
Intersubunit bridge B6	L19 (N)	2	L24E (T)	2 or 5	L19 and L24E are dissimilar at the sequence level. Both L19 and L24E, however, donate two β -strands in a similar way, to form an interprotein β -sheet with S14.

^aFold classes are according to the SCOP database (Andreeva et al. 2004) as follows: 1, all α ; 2, all β ; 3, α/β ; 4, $\alpha + \beta$; 5, folds dominated by a ligand or a metal ion.

mostly via helices 21, 22, and 25 (numbering as in Agalarov et al. 2000), which do not belong to Min rRNA. I included S8 in Min1/Min2 because it has PPL1 and bridges, via multiple protein–protein interactions, the Min1 members S2 and S17 (Fig. 3). Interestingly, a bacterial-like S8 homolog is encoded by the nuclear genome of *Caenorhabditis elegans* (F53A3.3; gi 2429452). It most likely operates in mitochondria, but nematode mitochondrial RNA appears to lack the targets of S8

interaction. Perhaps missing RNA segments are functionally replaced by extra proteins in nematode mitochondrial ribosome. Several hundred poorly characterized proteins in *C. elegans* are predicted to encode mitochondrial targeting peptides, and some of these proteins contain putative nucleic-acid-binding domains with S4, KH, or Ob folds (A. Mushegian, unpubl. observations). It would be interesting to know whether any of them are found within nematode mitochondrial ribosomes.

FIGURE 3. Interactions of bacterial SSU protein S8 with rRNA and Min1 proteins. The coordinates of *Thermus* SSU components are from PDB entry 1FJG. Helices (H) are numbered according to Agalarov et al. (2000) and Mears et al. (2002). For details, see text.

I reconstructed the protein complement of minimal and ancestral ribosomes by comparative analysis of sequences, structures, and phyletic patterns of ribosomal components. In all divisions of Life combined, there are at least 60 nonorthologous ribosomal proteins. One result of this work is that both Min and Anc sets contain a large fraction of those proteins—at least 35 in Min2 and ~40 in Anc. Some of the Anc components are shared by all present divisions of Life, while others are arranged in pairs, in which a bacterial/organellar form and an archaeal/eukaryotic form displace each other. It is not clear which of these alternative forms, or maybe their RNA counterpart, was present in LUCA. Almost all of these displacements were noticed by Harms et al. (2001) or by Klein et al. (2004). Harms et al. did not consider evolutionary implications, and Klein et al. interpreted gene displacements between ribosomal proteins as the direct evidence that in LUCA the role of each such protein had been played by rRNA. In contrast, I suggest that both RNA–protein and protein–protein displacements have been possible in the evolution of ribosome. It would be interesting to try engineering some of them using the present-day ribosomes.

Full activity of a ribosome requires several types of covalent modifications of rRNA and proteins. Although these factors were not analyzed in detail here, it is notable that most reconstructions of minimal and ancestral gene sets include at least one pseudouridylylase, several RNA methyltransferases, and chaperones that mediate ribosome

maturation (Anantharaman et al. 2002; Koonin 2003; Mushegian 2004).

Among the ancestral ribosomal proteins, there are representatives of all currently recognized classes of protein structures (Andreeva et al. 2004). Notably, however, in both Min2 and Anc sets, the all- α proteins and small ligand-dominated proteins are underrepresented, and proteins enriched in β -sheets are overrepresented, compared to ribosomal proteins as a whole (see Supplementary Material, at <http://research.stowers-institute.org/bioinfo>). This may have interesting implications for the origin and evolution of pre-LUCA ribosomes and proteins in general. As a more practical matter, the Min and Anc sets outlined here provide a blueprint to begin engineering a minimal ribosome in earnest.

MATERIALS AND METHODS

The outline of the approach is as follows. A trait (e.g., gene) is “minimal” (Min) if an organism needs this gene for survival. A gene in a present-day species is “ancestral” (Anc) if a particular ancestor of the species had an ortholog of this gene.

This work relies on the Min-rRNA model. I use Min-rRNA as it has been defined by Mears et al. (2002). Sequences of rRNAs with known three-dimensional structure were aligned to the nematode mitochondrial rRNA using the utilities at the CRW resource (Cannone et al. 2002) and manually edited to reflect the model, as depicted in Figure 3 of Mears et al. (2002). To define RNA–protein interactions, I used PDB entries 1FJG (*Thermus thermophilus* small ribosomal subunit) and 1S72 (*Haloarcula marismortui* large subunit) and computed all cases when at least one atom in a polypeptide chain was within 3.5 Å from any atom of rRNA. Though only one such pair of atoms was required for registering a protein–RNA interaction, in fact all interactions detected in that way involved multiple amino acids in one protein and, for each interacting protein, multiple bases in rRNA. Bridging by water or inorganic ions was not considered. Methods of sequence and structure comparison and phylogenetic inference are discussed in more detail in the Supplementary Material (<http://research.stowers-institute.org/bioinfo>).

The first goal of this work is to reconstruct the Min set of ribosomal proteins. Mears et al. (2002) listed 22 proteins that have orthologs in 3P2O–13 in SSU and 9 in LSU. A recount indicates that the list of ribosomal proteins found in 3P2O is longer, and yet, I propose that only some of these proteins are truly Min, namely, those that have cognate interaction sites in Min rRNA. The intersection of omnipresent proteins and proteins that bind Min rRNA gives the Min1 set of ribosomal proteins. Next, this set is supplemented with isofunctional proteins, i.e., nonorthologous counterparts in Bacteria and Archaea that interact with orthologous regions of rRNA in a similar way. Addition of these proteins produces Min2, the current estimate of the protein complement of minimal ribosome.

To reconstruct the Anc set, a specific ancestor has to be fixed. I focus on the common ancestor of the B and AE branches, called LUCA, the Last Universal Common Ancestor (Forterre and Philippe 1999; Mirkin et al. 2003). Because any protein belongs to one of four categories—Min+Anc+, Min–Anc–, Min+Anc–, Min–Anc+—one can proceed from Min2 to LUCA ribosome by finding Min+Anc– proteins and removing them from Min2, and

then finding Min–Anc+ proteins in the databases and adding them to the final list (Figure 1). Both steps rely on examination of the phylogenetic trees and phyletic patterns of all ribosomal proteins.

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ARCADY MUSHEGIAN

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