Chapter 1

A Comparative Perspective on Ribosome Biogenesis: Unity and Diversity Across the Tree of Life

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Abstract

Ribosomes are universally conserved ribonucleoprotein complexes involved in the decoding of the genetic information contained in messenger RNAs into proteins. Accordingly, ribosome biogenesis is a fundamental cellular process required for functional ribosome homeostasis and to preserve satisfactory gene expression capability.

Although the ribosome is universally conserved, its biogenesis shows an intriguing degree of variability across the tree of life. These differences also raise yet unresolved questions. Among them are (a) what are, if existing, the remaining ancestral common principles of ribosome biogenesis; (b) what are the molecular impacts of the evolution history and how did they contribute to (re)shape the ribosome biogenesis pathway across the tree of life; (c) what is the extent of functional divergence and/or convergence (functional mimicry), and in the latter case (if existing) what is the molecular basis; (d) considering the universal ribosome conservation, what is the capability of functional plasticity and cellular adaptation of the ribosome biogenesis pathway?

In this review, we provide a brief overview of ribosome biogenesis across the tree of life and try to illustrate some potential and/or emerging answers to these unresolved questions.

Key words Ribosome biogenesis, Ribosome assembly, rRNA, Maturation, RNA modifications, Eukaryotes, Archaea, Bacteria, Tree of life, Comparative biology, Evolution, Adaptation

1 In Search of Unity?

From an historical perspective, the search for unifying concepts in Science in general and in Biology in particular has been a key step to our fundamental and general understanding of molecular processes across the tree of life [1–7]. This idea can be easily grasped by famous aphorism variations around this theme: "From the elephant to butyric acid bacterium—it is all the same!" ([8], cited in [2]) or "Anything found to be true of *E. coli* must also be true of elephants" (attributed to Jacques Monod, 1954 [2]). However, there are also valid arguments to think that elephants and bacteria are characterized, to some extent, by distinguishable biological properties. Accordingly, molecular processes, including ribosome

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biogenesis, have been dissected from two albeit different and in part contra intuitively but cross-fertilizing viewpoints: a unifying and a dividing functional perspective [9–11]. As such comparative—ribosome biogenesis—biology may be torn apart between defining the real weight of functional similarities and differences which biological systems may adopt. In any case, these similarities and differences can only be appreciated in the light of detailed knowledge about the scrutinized biological system across a larger number of entities.

In this chapter, we attempt to provide a short comparative overview on the molecular principles required for ribosome biogenesis. In addition, we like to highlight few challenges and surprises that may alter our unifying/differential view on ribosome biogenesis across the tree of life.

2 Ribosome Biogenesis

2.1 Once Upon a Time . . . Ribosome Basic Facts

Ribosomes are universally conserved ribonucleoprotein particles allowing the decoding of the genetic information carried within messenger RNAs into amino-acid chains, the proteins [12]. Cytosolic ribosomes are composed of two ribosomal subunits, the small and the large ribosomal subunit (SSU and LSU, respectively) [12]. Strikingly, ribosomes are formed around a universally conserved structural core composed of three ribosomal RNA (rRNAs) molecules and 33 universally conserved ribosomal proteins (r-proteins) [13, 14]. Cytosolic ribosomes isolated from prokaryotic and eukaryotic organisms differ by the numbers and composition of their structural components, the r-proteins and rRNAs. Typically, cytosolic bacterial and archaeal 70S ribosomes are formed by the 30S (SSU) and 50S (LSU) ribosomal subunits [15–17]. Those are themselves composed of varying amounts of r-proteins (Figs. 1 and 2) which interact with the SSU 16S rRNA and LSU 23S and 5S rRNAs. These rRNAs also present various degree of organism's specific sequence size variations [54–56].

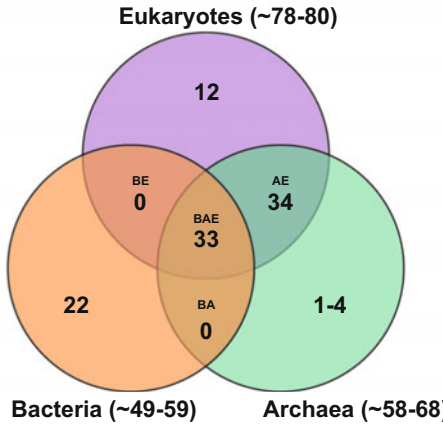
In eukaryotic cells, cytosolic 80S ribosomes are formed by the 40S (SSU) and 60S (LSU) ribosomal subunits [57, 58]. Concerning the amounts of ribosomal proteins, eukaryotic ribosomal subunits show also some, however less pronounced intra domain variations, compared to those observed across the bacterial and archaeal kingdoms (Figs. 1 and 2) [13, 14]. A striking feature of eukaryotic ribosomes is the presence of longer and additional rRNAs, the SSU 18S rRNA and the LSU 25/28S, 5.8S and 5S rRNAs [44, 59, 60].

In eukaryotes, rRNAs size expansion occurs by virtue of incorporation of additional rRNA sequences, the expansion segments, within the universally conserved prokaryotic-like rRNA core [23, 24, 61]. These expansion segments are varying in size and composition across eukaryotes [23, 24, 61, 62] and may have

a

	Bacteria	Archaea	Eukarya
rDNA repeats numbers [1]	1-16	1-4	150-200 (> 1,000 in plants)
rRNAs	16S, 23S and 5S	16S, 23S and 5S	18S, 25/28S, 5.8S and 5S
rRNA expansion segments [2]	yes (uncommon)	yes (variable - only few)	yes (variable amounts and length)
ribosomal proteins [3]		33 universal r-proteins	
	≈49-59 44 ubiquitous	≈58-68 54 ubiquitous / 71 described	≈78-80 78 ubiquitous
in vitro reconstitution [4]	yes	yes	no*
rRNA modifications [5]	protein-based (≈36 modif)	protein- and sRNP-based	protein- and sRNP-based
2´O-Methylation / Pseudourydilation	4/11	Sso (67/9); Hv (4/2) 7-127 C/D box sRNA	Sc (55/49); Hs (94/95)
additional "stand-alone" base modifications	≈ 20	Hv (7)/Tko (>100)	12
Ribosome biogenesis factors [6]	≈ 50	>40?	>200

b



c

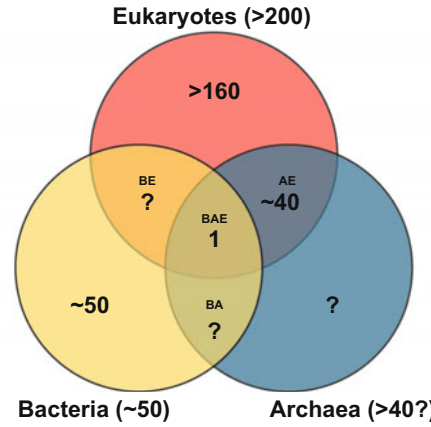


Fig. 1 | Ribosome and ribosome biogenesis key features overview across the tree of life. (**a**) Summary of ribosome and ribosome biogenesis key features. Modified from [18] according to [1] [19–22]; [2] [23–27]; [3] [13, 14, 28]; [4] [29–35]; [5] [36–43]; [6] [10, 44–48]. Sso—*Saccharolobus solfataricus*; Hv—*Haloferax volcanii;* Tko—*Thermococcus kodakarensis;* Hs—*Homo sapiens*; Sc—*Saccharomyces cerevisiae*. (**b**, **c**) Summary of shared ribosomal proteins (**b**) and ribosome biogenesis factors (**c**) across the three domains of life. Numbers of r-proteins and putative ribosome biogenesis factors sequence homologues shared between bacteria, archaea, and eukarya (BAE); bacteria, archaea (BA), archaea and eukarya (AE), bacteria and eukarya (BE), or unique to bacteria (B), or archaea (A), or eukarya (E), are indicated [based on [10, 13, 14, 28, 41, 44–51] and our unpublished results]. (Modified from Londei and Ferreira-Cerca [52])

originated early on during rRNA evolution, since some progenitors of these expansion segments have been traced within modern archaeal but also in some case in bacterial rRNAs [23–25, 63–66].

The diverse composition of r-proteins which is, up to now, apparently more predominant in bacteria and archaea [13, 14, 55], could indicate that in these cellular contexts, ribosome assembly, that is, the assembly of r-proteins with the rRNAs, and ribosome function may tolerate a higher degree of flexibility than in most eukaryotes. It is also interesting that reductive evolution (loss) of r-proteins seems to prevail in archaea [13, 14, 25].

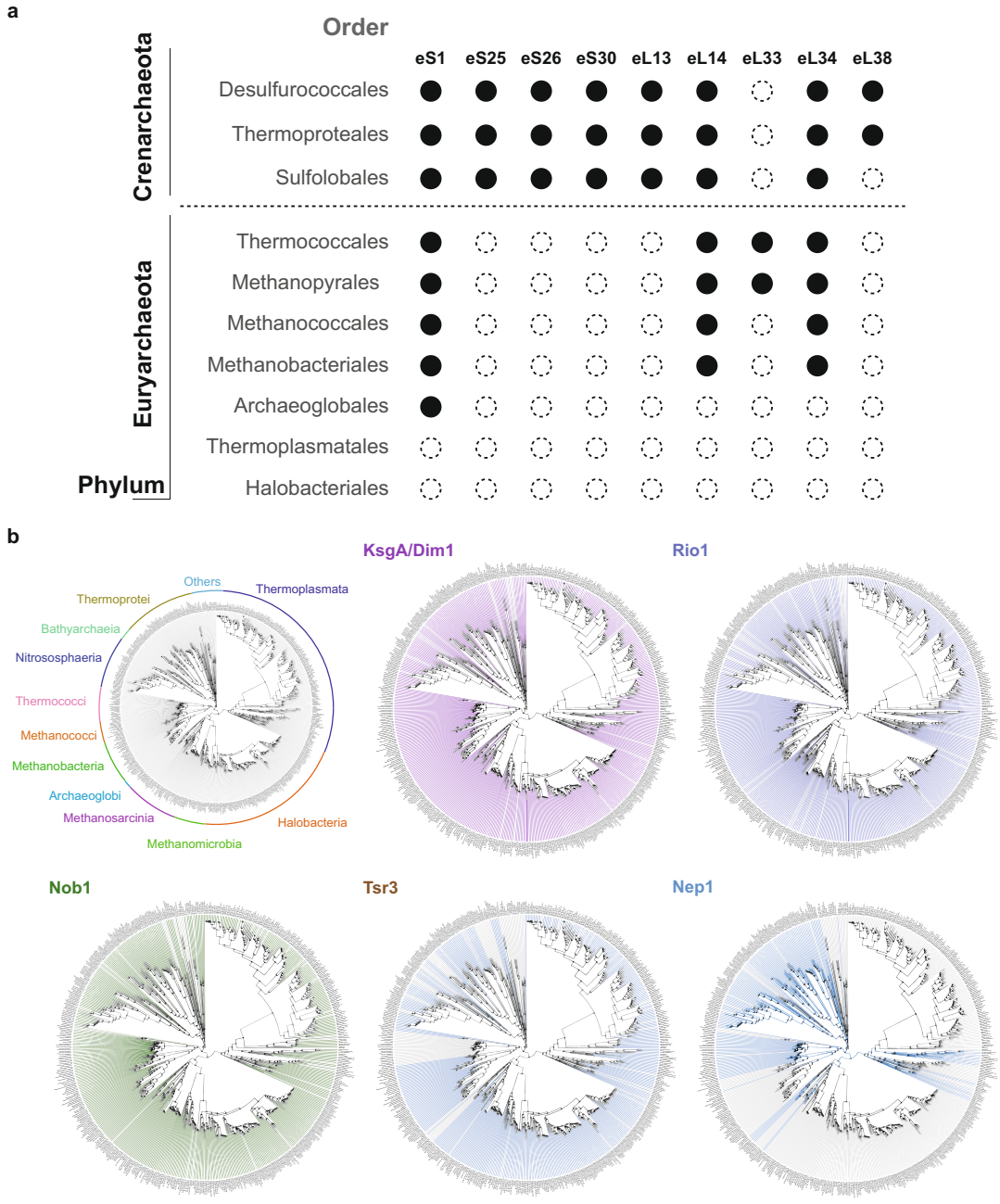


Fig. 2 | Exemplary conservation of selected ribosomal proteins and putative ribosome biogenesis factors involved in small ribosomal subunit biogenesis in archaea. (**a**) Exemplary repartition of selected archaeal ribosomal proteins shared between archaea and eukaryotes across two major archaeal Phyla. Black circle denotes the presence, and open circle denotes the absence of sequence homologue for the indicated ribosomal protein of the small (S) or large (L) ribosomal subunits, respectively (adapted from [13, 14] using the nomenclature proposed in [49]). (**b**) Phylogenetic conservation profile of the indicated known or putative small ribosomal subunit ribosome biogenesis factors across 1500 archaeal genomes were generated using AnnoTree (http:/annotree.uwaterloo.ca) [53]. Archaeal classes are annotated in a phylogenetic tree (upper left) as provided by AnnoTree. Note the absence of significant homology for Nep1 (e.g., Thermoplasmata, Halobacteria and more) or Tsr3 (e.g., Thermococcales) in a large group of organisms, in contrast to the more widespread distribution of KsgA/Dim1, Rio1, and Nob1 archaeal homologs. Modified from Londei and Ferreira-Cerca [52]

From a compositional point of view archaea and eukaryotes do share common r-proteins which are absent in bacteria, whereas bacteria do possess domain specific r-proteins [49, 61]. This correlates with the increased structural similarities between archaeal and eukaryotic ribosomal subunits in comparison to their bacterial counterparts [25, 61, 67].

This structural similarity has been observed early on by the group of James Lake, using electron microscopy, thereby, suggesting a closer evolutionary relationship of archaea and eukaryotes [15, 67, 68]. Recent phylogenetic analysis [69–71] and higher resolution structure analysis of ribosomal subunits [25, 61, 67] essentially confirm this idea but also provide additional insights into structural differences between the different domains of life, like for example differences in the peptide exit tunnel geometry [72], or species-specific structural alteration which may be related to organism-specific environmental adaptations [62, 73].

3 The Ribosome Assembly Process

The ribosome assembly process, that is, the assembly of r-proteins with rRNAs, has been analyzed very early in the history of ribosome research. Early work from the Nomura laboratory in the 1960–1970s aiming to understand the individual contribution of the r-proteins/rRNA to the protein synthesis process, has led to the first in vitro reconstitution of bacterial ribosomal subunits from its isolated structural components [29, 30, 74–77]. These studies were then followed by r-proteins omission experiments which culminated in the establishment of the first ribosomal proteins assembly maps describing r-proteins assembly dependencies [29–31]. Beyond being biochemical masterpieces, these studies have revealed key features of the ribosomal assembly process in bacteria. Notably, the self-assembling nature of ribosomal subunit formation, and the fact that ribosome assembly proceeds via a combination of cooperative and hierarchical mechanisms [29–31, 78, 79]. However, these in vitro assembly experiments have been mitigated by the fact that they occur under nonphysiological conditions, thereby suggesting the existence of in vivo facilitating mechanisms which were discovered later [29–31, 78, 79]. Remarkably, in vitro reconstitution of ribosomal subunits has not only been achieved using structural components isolated from different bacterial sources, but also from two evolutionary divergent representative archaea [32–34]. In contrast, similar in vitro reconstitution of eukaryotic ribosomal subunits solely using purified structural components has not been accomplished to date.

Despite this fundamental biochemical difference, some aspects of ribosome assembly in bacteria and eukaryotes follow rather similar molecular principles, for example the hierarchical and

cooperative assembly, or stepwise stabilization of r-proteins [18, 78–87]. Together these similarities suggest that ribosome assembly has likely evolved around a self-assembling (presumably self-replicating) ancestor ribosome [26, 88], which has retained some of its original assembly properties and constraints. Not surprisingly, some of these ancestral properties/constraints are most probably universally shared. In addition, existing molecular mechanisms have been modified (adapted or optimized), new ones implemented, or some maybe lost, due to organisms or common ancestor specific requirements. All these evolutionary contributions are not trivial to disentangle, but functional and structural analysis of the ribosome assembly pathway, in model and probably most importantly in nonmodel organisms, will help us to further clarify the inherited molecular constraints and properties underlying the assembly of ribosomal subunits.

4 Facilitating Ribosome Assembly

As mentioned above, efficient ribosome assembly in vivo depends on ribosome biogenesis factors which are collectively believed to facilitate various aspects of the ribosome biogenesis process [44, 59, 60, 78, 79]. These ribosome biogenesis factors can be subdivided into different protein classes according to their respective structural organization and/or enzymatic activity. For example, ribosome biogenesis progression depends on the presence of energy consuming enzymes, like GTPases, ATPases (AAA ATPase, RNA helicase, etc.). However, it is important to note that the ensemble of ribosome biogenesis factors differs in numbers and nature from bacteria to eukaryotes [10, 18, 44, 59, 60, 78, 79] (Fig. 1). Accordingly, the relative domain-specific repartition of structural features and/or enzyme activities implicated in ribosome biogenesis progression may vary considerably between different groups and may reflect functional adaptations within the different domains of life. For example, GTPases seem to be enriched in the bacterial ribosome biogenesis pathway, whereas ATP-dependent processes, or β-propeller containing proteins are enriched in the eukaryotic ribosome biogenesis context [10, 18, 44, 59, 60, 78, 79].

In fact, and with the exception of the (almost) universally conserved dimethyl-transferase KsgA/Dim1 [89, 90], ribosome biogenesis factors are not well conserved between bacteria and archaea or between bacteria and eukaryotes [18, 45]. In contrast, a substantial portion of eukaryotic ribosome biogenesis factors are found in archaeal genomes even though our understanding of their respective functions in archaea remains still limited [45]. Nevertheless, we and others could demonstrate some functional analogy with their eukaryotic counterparts in vivo and/or in vitro [18, 91–93]. These observations suggest that probably more

(if not most) of these eukaryotic-like ribosome biogenesis sequence signatures present in archaea might be authentic ribosome biogenesis factors shared between archaea and eukaryotes. In comparison, eukaryotic ribosome biogenesis is characterized by a large increase of eukaryotes-specific ribosome biogenesis factors (>200) [46, 59, 60]. The functional requirements for this "sudden" increased complexity of eukaryotic ribosome biogenesis remains to be fully understood (Fig. 1).

In addition, to composition and number variations observed in bacteria, archaea, and eukaryotes, organisms specific variations can be observed [18, 36, 45, 90, 94, 95]. For example, the set of ribosome biogenesis factors vary across the archaeal phylum and seems to follow the general trend of reductive evolution previously observed for archaeal r-proteins (Fig. 2) [13, 14, 52]. In eukaryotes, ribosome biogenesis factors diversity further increases from unicellular to multicellular eukaryotes with the addition of factors implicated in ribosome biogenesis [46, 59, 60]. Moreover, recent studies have provided new insights into ribosome biogenesis plasticity thereby suggesting that the order of functional requirement of some assembly factors/r-proteins can vary or be functionally bypassed in some conditions [90, 96–100].

These observations have various implications for our understanding of ribosome biogenesis evolution and plasticity. For one, the presence/absence of certain molecular components can be tolerated owing that the proper rescue mechanisms are implemented (coevolving). Furthermore, these imply a higher functional plasticity of the order of events within the ribosome biogenesis pathway, whereby an alternative assembly landscape might be used or kinetically favored depending on the cellular context [81, 87, 98, 101]. However, it should be noted that this apparent diversity/plasticity may still converge to the formation of essential assembly intermediates that are functionally and/or structurally equivalent, thereby fulfilling critical inherited molecular events required for ribosome biogenesis.

Accordingly, and despite differences in the nature and amounts of the ribosome biogenesis factor ensemble, it is conceivable that the core function supported by some or all ribosome biogenesis factors are functionally equivalent across the tree of life, thereby suggesting evolutionary constraints which would have favored the establishment of dedicated functional mimicry rather than functional divergence around the universal ribosome core [18]. It is for example striking, that some divergent ribosome biogenesis factors implicated in the formation of the SSU in model bacteria, archaea and eukaryotes, are binding at very similar locations within the nascent pre-ribosomal subunits and may fulfill similar molecular tasks (see further discussion in [18]). For instance, the SSU rRNA 3′ end processing follows a very similar pattern which involves a KH-domain containing ribosome biogenesis factor which interact

and presumably stabilized the 3′ end of the 16S/18S rRNA, thereby enabling efficient and presumably controlled endonucleolytic cleavage. In *E. coli*, the Era GTPase, which contains a KH-domain [102–104] interact with the endonuclease YbeY and the r-protein uS11 [105], thereby facilitating 3′ end maturation. In eukaryotes, Pno1/Dim2, a KH-domain containing protein, interacts with the endonuclease Nob1 and both are located in proximity of uS11. Moreover, mutational analysis revealed functional implication of uS11, Pno1/Dim2 and Nob1 for 18S rRNA maturation [106–110]. Furthermore, archaeal homologues for Pno1/Dim2, Nob1 and uS11 are present in most archaeal genomes [111]. Considering that both the endonucleases and KH-domains (type I vs. type II) are evolutionary distinct and presumably unrelated, these observations suggest a functional convergence/mimicry at the basis of the maturation of the 16S/18S rRNA 3′ end. Whereas, the origin of this divergence at the molecular level is poorly understood, evolutionary constraints have remarkably selected a very similar mode of action in its principle (see further discussion in [18]).

Further supporting the existence of functional convergence enabling ribosomal subunit synthesis, we and others have proposed that pseudocircularization events might represent an early common feature of ribosomal subunits biogenesis [82, 112, 113]. However, the implicated molecular machineries are to some extent very different.

In prokaryotic organisms, stabilization of the 5′-3′ mature ends of the nascent rRNA precursors in a topologically limited environment is enabled by the formation of double-stranded RNA structures, the processing stems [114–121]. In all archaeal organisms analyzed so far, this environment is further stabilized by the formation of a true covalent circularization of the pre-rRNA, in form of precircular rRNA intermediates [112, 122, 123]. Finally, in eukaryotes, recent cryo-EM studies have revealed stabilization of a pseudocircular intermediate of the pre-LSU [124]. The formation of this intermediate requires the participation of a distinct eukaryotes-specific ribosome biogenesis subcomplex which may stabilize the LSU root helix bundle prior to the assembly of the universally conserved r-protein uL3 [124, 125]. Noteworthy, early maturation of the pre-23S rRNA by mini-RNase III, which liberates the nascent 23S rRNA from its processing stem in *B. subtilis*, is stimulated by the presence of uL3 [126]. In addition, uL3 is critical to initiate in vitro assembly of bacterial 50S [127, 128].

In the case of the SSU, the snoRNA U3 and its associated proteins provide a scaffold that brings distant rRNA elements in close proximity within an encapsulated environment described as for the 90S/SSU Processome [129–131]. However, the relative orientation of the future mature 5′-3′ ends in these structures is not resolved.

Finally, the formation of the SSU central pseudoknot is a universal feature required for SSU biogenesis and function [132, 133]. In eukaryotes, its formation is facilitated by the snoRNA U3, which is not present in bacteria and archaea [44, 59, 60, 134, 135]. However alternative (U3-independent) mechanisms, enabling the formation of the SSU central pseudoknot in these cellular contexts have been proposed [135–138]. For example, sequences present in the 5′ end of the pre-16S rRNA show potential complementarity, similar to U3, which could hybridize with the region required for central pseudoknot formation [136, 139–141].

5 Processing and Modifications of Ribosomal RNA

Concomitantly to the assembly process, rRNAs are matured by ribonuclease activities and modified at various positions [18, 37, 44, 59, 60, 78, 79, 114, 142].

Despite billion years of independent evolution most rRNAs are predominantly transcribed as a polycistronic operon [19]. It is believed that this organization is required for the efficient coordinated assembly of ribosomal subunits. However, this idea has been challenged on the one hand by the presence of naturally occurring independent rDNA production units, and on the other hand, by early genetic engineering experiments which have successfully separated the polycistronic eukaryotic SSU and LSU rRNAs [143, 144]. The immature precursor-rRNA contains flanking regions that need to be matured by the action of various ribonucleases. These maturations events are timely ordered during the ribosomal subunit biogenesis process. This relative ordering presumably depends on specific ribosomal subunit assembly statuses which in turn control substrate accessibility or its relative positioning [18, 37, 44, 59, 60, 78, 79, 114, 143, 145]. The inherent irreversible property of these processing steps may also impose various degrees of "quality control" constraints to the ribosome biogenesis process in order to avoid the irreparable formation of improperly assembled pre-ribosomal subunits.

Similar to the ribosome biogenesis factors, the set of ribonucleases used in bacteria, eukaryotes and presumably in archaea are not well conserved between these domains [18, 37, 44, 59, 60, 78, 79, 94, 114, 142]. In bacteria, whereas promiscuous ribonucleases are used, eukaryotic cells have developed a set of specific enzymes to mature their rRNAs, some of which are also present in archaea [18, 37, 44, 52, 59, 60, 78, 79, 94, 114, 142]. Based on our current knowledge, it is difficult to properly extract functional similarities between the different biological systems. However, we have previously noticed some peculiar common molecular

principles required for the maturation of the SSU rRNA 3′-end (see above and [18]). However, additional structural and functional information capturing these events "in action" will be necessary to provide invaluable insights into the structural properties of their respective substrates [145].

Since the 1950s, ribosomal RNA modifications, which are mostly concentrated within or closed to the ribosomal subunit functional centers, have been known [37, 146, 147]. These modified rRNAs residues are found, to various extents, in all domains of life [37–40]. However, the mechanisms by which these modifications are added diverge across the tree of life. On the one hand, bacterial rRNAs are modified by stand-alone enzymes that are dependent on a specific assembly status to recognize and modify their respective substrates. On the other hand, and in addition to stand-alone enzymes, archaea and eukaryotic organisms utilize an RNA-guided modification machinery, whereby RNA-protein complexes carrying methyltransferase or pseudouridylation activity are formed (C/D and H/ACA snoRNPs, respectively). In this context, the RNA part, which contains a sequence complementary to the targeted rRNA region, guides the enzymatic activity to its substrate [37, 39, 40, 148–150] (Fig. 1).

These different modes of action have important consequences regarding substrate recognition, timing of modifications and structural constraints that may be imposed by the formation of snoRNA::rRNA duplexes during ribosome assembly, and have thereby probably (re)shaped several aspects of the ribosome biogenesis pathway [18, 37]. Whereas the relative positions of the conserved modified residues are usually similar, the nature of the modification itself may vary across the tree of life [18, 151]. Finally, rRNA modifications appear to be dynamic across the tree of life, whereby significant variation in nature and number of modifications is observed, and may also vary during the organisms life time [36, 38, 39, 41, 90, 152, 153]. These variations may not only influence ribosome function but also the ribosome biogenesis pathway itself [18, 38, 39, 90, 154].

6 Learning from Organelle Ribosome Biogenesis?

Eukaryotic organelles also contain ribosomes, which are very distinct from cytoplasmic ribosomes. Organelle's ribosomes and their ribosome biogenesis pathways, which have not been discussed so far, may represent important resources to better extricate key ribosomal subunits biogenesis features. Organelle ribosomal subunits are interesting from several perspectives. First, the ribosomal subunits composition is rather diverse across different organisms. Second and in contrast to cytosolic ribosomal subunits, organelle ribosomal subunits contain a reduced amount of rRNA over

r-proteins. Third, organelle ribosomal subunits contain organelle-specific ribosomal proteins, expending the possible diversity of the ribosome assembly landscape. These r-proteins may replace lost rRNA elements or stabilize the reduced rRNA core. Fourth, organelle ribosomal subunits have followed complicated independent evolutionary trajectories enabling the formation of ribosomal subunits optimized for the translation of a limited set of mRNAs [49, 155–157]. In addition to ribosome biogenesis factors shared between bacteria and organelles, recent studies have revealed the existence of specific dedicated multiprotein machineries required for the progression of organelle ribosome biogenesis [155, 158–166]. Despite this apparent sequence/structural specificity, intriguing functional similarity between cytosolic and organelle ribosome biogenesis pathway has been proposed. Altogether, these results suggest that despite very different evolutionary path ribosomal subunits biogenesis may proceed via functionally equivalent assembly intermediates and requires similar but diverse functional innovations facilitating ribosomal subunits assembly [155, 158–166]. Lessons from these and future studies will certainly reveal new insights on the evolution and adaptation of ribosomal subunit biogenesis.

7 Concluding Remarks

Despite undeniable differences between the ribosome biogenesis pathways as known from various model organisms, it is striking that some (key) ribosome biogenesis features have been maintained across billions of years of evolution. However, the evolutionary events which have led to components diversification while conserving functional similarities instead of consolidating a core of conserved ribosome biogenesis components remain rather enigmatic. Moreover, the extent of true functional divergence or functional convergence, along the ribosome biogenesis pathway, needs to be properly identified, promising exciting perspectives and challenges for comparative ribosome biology analysis in the future. Correspondingly, in the recent years metagenomics have revealed an unexpected microbial biodiversity [167], which awaits its biochemical and functional examination, and will certainly provide new insights into conserved principles of ribosome biogenesis.

In addition, our increased understanding of supposedly simplified ribosome biogenesis pathway present in symbionts, organelles, and organisms harboring reduced genomes, which for simplicity is not discussed in depth, will provide supplementary functional insights into common and specific principles of ribosome biogenesis [47, 55, 62, 160–162, 168].

Finally, thanks to the massive development in the field of genetic engineering we are probably at the very beginning of a massive biological revolution, which will ease the characterization of nonmodel organisms, to develop synthetic biology approaches, and to uncover some of the most fundamental secrets of life. How we will deal with this information will however be crucial to leverage the significance of these discoveries for our understanding of ribosome biogenesis. When reaching this point, emphasis toward functional similarity and diversity of the ribosome biogenesis process, or its plasticity, will have to be carefully appreciated and will require to understand the genuine functional implication of these molecular features across different organisms' lifestyle and organisms' specific evolutionary history [169].

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