Conserved ribosomal RNA modification and their putative roles in ribosome biogenesis and translation

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Abstract

rRNA maturation requires extensive covalent modifications of riboses and bases. These modifications concern exclusively the most conserved regions of the molecule, and some modifications are highly conserved throughout the evolution. In bacteria, rRNA modification is achieved exclusively by site-specific enzymes while in archaea and eukaryotes the formation of 2'-*O*-methylriboses and pseudouridines is guided by numerous snoRNA that direct a catalytic machinery to the target sites on the pre-rRNA. The exact function of these modifications remains elusive since preventing their formation generally leads to no detectable phenotype. However, most of the enzymes that catalyze the formation of these modifications are encoded by essential genes in yeast. Moreover, in some cases preventing the formation of several modifications simultaneously affect ribosome biogenesis and translation. This review presents rRNA modifications that have been conserved throughout the evolution and it gives a special emphasis to the recently characterized 2'-*O*-ribose RNA methyltransferase Spb1p, which broke the "snoRNA-guided only" methylation dogma.

1 Introduction

Ribosomes are large ribonucleoprotein complexes whose main function is to translate the genetic information into proteins. The ribosome controls translation fidelity by ensuring that the proper tRNA is selected in front of a given codon. Then, the ribosome catalyzes the polymerization of proteins by transferring the elongated polypeptide chain from the peptidyl-tRNA present in the P-site to the incoming aminoacyl-tRNA present in the A-site of the ribosome. The peptidyl transferase reaction is catalyzed by the ribosomal RNA, as foreseen long ago (Crick 1968), and then demonstrated year after year from photocrosslinking of derivatives of tRNA to rRNA (Barta et al. 1984), to the discovery that deproteinized rRNA from the large subunit is sufficient to achieve the peptidyl transfer reaction (Noller et al. 1992). Later, these results were confirmed by showing that there is no protein in the catalytic center of the ribosome (Ban et al. 2000) and that an

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adenine of the large rRNA is likely directly involved in the catalytic reaction (Nissen et al. 2000).

Ribosomes from prokaryotes and eukaryotes share numerous features that form the core elements. Since all ribosomes are able to polymerize proteins, it is assumed that the elements required for translation are present in the core elements. Throughout evolution, ribosomes have acquired additional RNA sequences and new ribosomal proteins. These additional elements are likely to be involved in other aspects of protein synthesis that might be important for more complex organisms. For instance, metazoans must synthesize many different kinds of proteins in different cell types and in a timely fashion. Also, larger ribosomes might be involved in mRNA localization, mRNA turnover, regulating translation or addressing proteins to certain cellular compartments.

A major difference between organelles, bacteria, and archaea on one side and eukaryotes on the other is that, in the latter, ribosomes are synthesized, assembled, and processed in a cellular compartment that is different from the one in which translation takes place. The increased complexity of ribosome biogenesis in eukaryotes is illustrated by the fact that the number of genes encoding nucleolar components is about twice the number of ribosomal components *per se*. Although ribosomes from organelles, bacteria, and archaea do undergo processing to become functional, it is simpler than in eukaryotes. In addition, it has been shown long ago that functional prokaryotic ribosomes could be assembled *in vitro* from their isolated constituents (Hosokawa et al. 1966), while this has not been achieved for eukaryotic ones. This result suggests that ribosome biogenesis in eukaryotes must follow an ordered pathway that includes some essential intermediate steps. It is likely that these steps require internal and external transcribed spacers and nucleolar components, which are not part of mature ribosomes. It is generally assumed that assembling ribosomes in the nucleus rather than in the cytoplasm may provide the cell various levels of control on their synthesis. Final processing stages occur in the cytoplasm, possibly to prevent the accumulation of functional ribosomes in the nucleus.

The extent of ribosome expansion during the evolution is quite significant and may account for the additional functions performed by ribosomes from higher eukaryotes, as mentioned above. However, this increase in size is not as spectacular as the enormous increase of the diversity of the proteins a ribosome might synthesize, as shown in Table 1. In contrast, the number of rRNA modifications increases very significantly, along with the complexity of the organism. For instance, it is quite striking that yeast mitochondrial ribosomes, which are required for the synthesis of ~ 10 proteins, are composed of mitochondrial rRNA that possess only three modifications. In contrast, ribosomes from metazoans synthesize tens of thousands of different proteins and contain ~ two hundred modified nucleotides. Nascent polypeptides exit from the ribosome through a tunnel that is ~ 15Å in diameter and 80% of the methylated nucleotides have been mapped to the inner face of this tunnel in *H. marismortui* (Nissen et al. 2000). The hydrophobic nature of the methyl groups may prevent the nascent polypeptide chain to stick to this tunnel. According to this view, the greater the complexity of a given organism's proteome, the higher the chance to encounter certain amino-acid motifs