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High-resolution structures of mitochondrial ribosomes and their functional implications

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Mitochondrial ribosomes (mitoribosomes) almost exclusively synthesize essential components of the oxidative phosphorylation machinery. Dysfunction of mitochondrial protein biosynthesis leads to human diseases and plays an important role in the altered metabolism of cancer cells. Recent developments in cryo-electron microscopy enabled the structural characterization of complete yeast and mammalian mitoribosomes at near-atomic resolution. Despite originating from ancestral bacterial ribosomes, mitoribosomes have diverged in their composition and architecture. Mitoribosomal proteins are larger and more numerous, forming an extended network around the ribosomal RNA, which is expanded in yeast and highly reduced in mammals. Novel protein elements at the entrance or exit of the mRNA channel imply a different mechanism of mRNA recruitment. The polypeptide tunnel is optimized for the synthesis of hydrophobic proteins and their co-translational membrane insertion.

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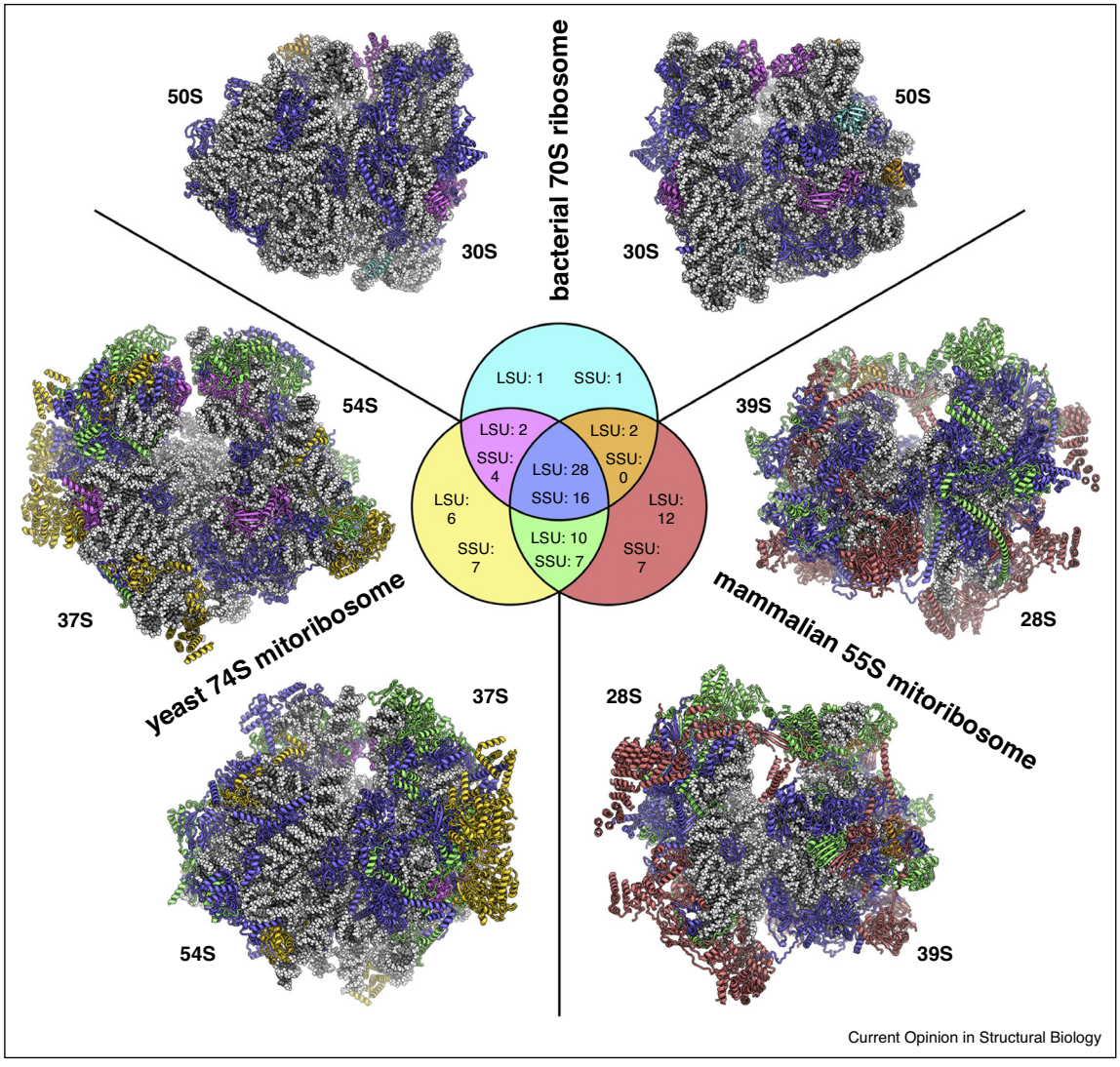
Introduction

Mitochondria are cellular organelles of endosymbiotic origin responsible for energy conversion and ATP production by oxidative phosphorylation (OXPHOS), which is catalyzed by large protein complexes in the inner mitochondrial membrane. Essential components of the OXPHOS complexes are encoded on the mitochondrial genome and synthesized by the in-house transcription and translation machinery [1,2]. Mitochondrial protein biosynthesis has evolved several unique aspects, including a reduced genetic code, an adapted regulation mechanism, and mitochondrial ribosomes (mitoribosomes) that are highly specialized in the synthesis of membrane proteins [3,4]. The first 3D reconstruction of the bovine mitoribosome at low resolution showed an overall shape that differs markedly from bacterial and eukaryotic cytoplasmic ribosomes [5]. Because crystallization approaches failed due to sample heterogeneity and low abundance of mitoribosomes, high-resolution structures were inaccessible until recent technical developments in cryo-electron microscopy (cryo-EM) [6,7]. In particular, the introduction of direct electron detectors enabled cryo-EM reconstructions of mitoribosomes at near-atomic resolution. The Ban and Aebersold laboratories used a combination of chemical cross-linking and mass spectrometry to interpret their cryo-EM map of the porcine mitoribosomal large subunit (LSU) at 4.9 Å resolution [8,9]. The Ramakrishnan and Scheres laboratories resolved the yeast mitoribosomal LSU at 3.2 Å resolution, allowing *de novo* building and refinement of a full atomic model [10]. The high-resolution structures of the porcine and human LSU at 3.4 Å resolution [11,12] and the complete mitoribosomes at 3.8 Å and 3.6 Å resolution [13••,14••] were determined subsequently. The recently published atomic model of the yeast mitoribosomal small subunit (SSU) completes the high-resolution structures of the yeast, porcine and human mitoribosomes [15••], which are the focus of this review. Furthermore, we will discuss the extreme evolutionary divergence of mitoribosomes and their unique structural features suited for mitochondrial-specific aspects of protein synthesis.

Evolutionary divergence of mitoribosomes

According to the endosymbiotic theory, mitochondria evolved by the engulfment of a bacterium by the eukaryotic progenitor cell [16,17]. Consequently, mitoribosomes are evolutionarily derived from ancestral bacterial ribosomes [18]. However, biochemical and initial structural studies [5,19] as well as the recent high-resolution structures [13••,14••,15••] show that in spite of their evolutionary origin, mitoribosomes have dramatically diverged from bacterial ribosomes and also between different eukaryotic lineages (Figure 1). In general, mitoribosomes contain a considerably increased number of ribosomal proteins [20,21] that form an extensive interaction network on the surface of the ribosomal RNA (rRNA) core [13••,14••,15••]. The rRNAs are highly variable in length and can either be extended as it is the case in fungi,

Figure 1



Evolutionary divergence of the yeast 74S and the mammalian 55S mitoribosomes compared to the contemporary bacterial ribosome. The atomic models of the bacterial 70S ribosome (*Escherichia coli*, PDB 4YBB) [53], the yeast 74S mitoribosome (*Saccharomyces cerevisiae*, PDB 5MRC) [15••], and the porcine 55S mitoribosome (*Sus scrofa*, PDB 5AJ4) [13••] are shown in two views related by a 180° rotation. The backbone and the bases of the rRNAs and the CP tRNA are represented as white and gray spheres, respectively. The ribosomal proteins are colored according to their species distribution. A diagram in the center indicates the number of proteins that are either shared between the yeast 37S, the mammalian 28S, and the bacterial 30S ribosomal small subunit (SSU) as well as between the yeast 54S, the mammalian 39S, and the bacterial 50S ribosomal large subunit (LSU) or that are specific for each type of ribosomes (color coded as in the structures).

plants, and most algae, or highly reduced, as in metazoans and kinetoplastids [22•].

In particular, due to its expanded rRNA, the presence of additional ribosomal proteins, and extensions of conserved ribosomal proteins, the yeast 74S mitoribosome composed of a 54S LSU and a 37S SSU has increased in molecular weight by 30% (0.7 MDa) in comparison to bacterial 70S ribosomes [10,15••] (Table 1). The rRNA expansion segments extend from the core and act as a scaffold for the newly recruited ribosomal proteins. In addition, large N- and C-terminal protein extensions increase protein interconnectivity.

In contrast, the mammalian 55S mitoribosome composed of a 39S LSU and a 28S SSU lacks these rRNA expansion segments and its rRNA is reduced to roughly half the size of bacterial rRNAs [3,5,11,12,13••,14••] (Table 1). Because of the increase in protein mass, mammalian mitoribosomes have an inverted RNA:protein ratio of 1:2 compared to the bacterial 70S ribosome and their proteins cover the core of the rRNA almost entirely.