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Review

Mammalian mitochondrial ribosomal small subunit (MRPS) genes: A putative role in human disease

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ABSTRACT

Mitochondria are prominently understood as power houses producing ATP the primary energy currency of the cell. However, mitochondria are also known to play an important role in apoptosis and autophagy, and mitochondrial dysregulation can lead to pathological outcomes. Mitochondria are known to contain 1500 proteins of which only 13 are coded by mitochondrial DNA and the rest are coded by nuclear genes. Protein synthesis in mitochondria involves mitochondrial ribosomes which are 55–60S particles and are composed of small 28S and large 39S subunits. A feature of mammalian mitoribosome which differentiate it from bacterial ribosomes is the increased protein content. The human mitochondrial ribosomal protein (MRP) gene family comprises of 30 genes which code for mitochondrial ribosomal small subunit and 50 genes for the large subunit. The present review focuses on the mitochondrial ribosomal small subunit genes (*MRPS*), presents an overview of the literature and data gleaned from publicly available gene and protein expression databases. The survey revealed aberrations in MRPS gene expression patterns in varied human diseases indicating a putative role in their etiology.

Contents

1. Introduction

Mitochondria are integral to a wide range of cellular functions under both physiological (ATP production, biosynthetic intermediates) and pathological conditions (autophagy and apoptosis). Mitochondria are of bacterial ancestry arising out of a putative symbiotic relationship between alpha-proteobacterium and eukaryotic progenitor. Mitochondria are comprised of an internal matrix enclosed by two separate and functionally distinct outer and inner membranes that encapsulate the intermembrane space. They also contain mitochondrial DNA (mtDNA),

Abbreviations: B-ALL, B Cell Acute Lymphoblastic Leukaemia; CRC, Colorectal Cancer; DS, Down's syndrome; ESCCs, Oesophageal Squamous Cell Carcinomas; IHC, Immunohistochemistry; MRP, Mitochondrial Ribosomal Protein; MRPS, Mitochondrial Ribosomal Small Subunit; mtDNA, Mitochondrial DNA; NSCLC, Non-Small Cell Lung Cancer; T-ALL, T cell Acute Lymphoblastic Leukaemia; TGCT, Testicular Germ Cell Tumors.

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transcription and translation apparatus required for protein synthesis (Nunnari and Suomalainen, 2012). An inventory of mitochondrial proteins indicates that mammalian mitochondria contain over 1500 proteins, which vary in a tissue-dependent manner. Because mtDNA encodes only 13 of these proteins, mitochondria depend on the nucleus and other cellular compartments for most of their proteins and lipids. Mitochondria contain macromolecular complexes comprising of subunits encoded by nuclear and mitochondrial DNA. Nuclear-encoded mitochondrial proteins are actively imported and sorted into each mitochondrial compartment (Kitakawa and Isono, 1991) (Pietromonaco et al., 1991). Human mitochondrial disorders are known to be caused by mutations in mitochondrial and/or nuclear DNA. Excellent articles on mitochondria and disease have reviewed the evidence, which indicate deregulated functions of mitochondria in several diseases (Taylor and Turnbull, 2005; Duchen, 2004; Dromparis and Michelakis, 2013).

The mitoribosome of mammals are 55-60S particles and are composed of small 28S and large 39S subunits (Pietromonaco et al., 1991). The human mitochondrial ribosomal protein gene family comprises of 30 genes which code for mitochondrial ribosomal small subunit and 50 genes for the large subunit as per the recently published literature on structure of mammalian mitochondrial ribosome and the HUGO gene nomenclature committee (http://www.genenames.org), and all of the Mitochondrial Ribosomal Proteins (MRP's) are encoded by nuclear genes. The unique protein rich composition of the mammalian mitoribosome has emerged through the recruitment of proteins coded by nuclear genes at the expense of rRNA, giving rise to an overall architecture divergent from that of either yeast or bacteria (Sharma et al., 2003). Detailed structural analysis of the mitochondrial ribosome performed using cryoelectron microscopy and the subsequent derived atomic model of the entire 55S mitoribosome in complex with mRNA and tRNA's have given us a fascinating glimpse on the functioning of mammalian mitoribosome. The structures revealed that mammalian mitochondrial ribosomes differ significantly from all other known ribosomes in that they are specialized to exclusively translate hydrophobic and integral membrane proteins. Unlike the cytoplasmic ribosomes they are permanently tethered to the mitochondrial inner membrane through MRPL45 protein of the large subunit. The high protein content of the human mitochondrial ribosome gives it a distinct shape which differs from that of bacteria or yeast, and is less compact than the cytoplasmic ribosome. The accessibility of the rRNA to solvent has been reduced to a large extent relative to the bacterial ribosome and is limited to the inner most core of the ribosome, whereas the proteins cover the surface of the ribosome at a distance away from the core. The reduced exposure could potentially help shield from reactive oxygen species (ROS), a major source of RNA damage that is elevated in the mitochondria as a by-product of oxidative phosphorylation. The two ribosomal subunits are connected by a number of intersubunit bridges which can be rearranged during conformational changes. Also, the interface of mammalian mitochondrial ribosome has greater number of protein mediated contacts, the net effect of which is greater conformational flexibility. The large subunit of human mitochondrial ribosomes comprises of two ribosomal RNA molecules the 16S and mitochondrial tRNA for valine along with 48 proteins. Significant features of the large subunit involve interactions with mitochondrial tRNA, the adaptation of the exit tunnel for hydrophobic nascent peptides, extensive remodeling of the central protuberance, the recruitment of mitochondrial valine transfer RNA (tRNA val) which plays an integral structural role. The 28S subunit comprises of 12S rRNA along with 30 proteins. The subunit plays a vital role in the translation of leaderless mRNA, selection of translation initiation site and is characterized by conformational flexibility during translation. Further, the subunit is distinguished from other ribosomes due to the intrinsic GTPase activity acquired through the GTP-binding protein, *MRPS29*. Despite the structural and compositional differences between the mammalian and bacterial ribosomes, functional aspects like peptidyl transferase activity and mRNA decoding centers are conserved and the functional similarity is significantly demonstrated by the off-targets effects of antibiotics classes like aminoglycosides (Greber et al., 2015), (Greber et al., 2014), (Amunts et al., 2015), (Brown et al., 2014) (Zhang et al., 2005).

Mutations or deficiencies of ribosome assembly proteins or other essential proteins involved in mitochondrial translation are potential candidates for mitochondrial diseases, since the mitochondrial ribosome translates mRNAs for the 13 essential components of the oxidative phosphorylation system. Excellent reviews published recently have addressed the structure of mitoribosome and its impact on the protein translation, mechanism of translation, translation factors which help constitute the mitochondrial translation machinery and implications for human disease (Lightowlers et al., 2014; Ott et al., 2016; De Silva et al., 2015; Boczonadi and Horvath, 2014). A prior review on mitochondrial ribosomal genes had highlighted their role in mitochondrial disease (Brien et al., 2005), the purpose of the present review is to focus on mitochondrial ribosomal small subunit genes (MRPS) and highlight their potential role in human disease.

2. Mitochondrial ribosomal small subunit genes and human disease

2.1. MRPS genes and salient features of SSU structure

The analysis of human mitochondrial small subunit had recorded 29 distinct proteins, fourteen of these proteins have homologues in *Escherichia coli* 30 S ribosomal proteins and more in *Drosophila melanogaster*, *Caenorhabditis elegans*, and Yeast. Fifteen of the MRPS proteins are specific to mammalian mitochondrial ribosomes (Cavdar Koc et al., 2001). In addition, 3 new proteins (*MRPS37* (Coiled-coil-helix-coiled-coil-helix domain containing protein 1-CHCHD1), *MRPS38* (Aurora kinase A interacting protein1, AURKAIP1), *MRPS39* (Pentatricopeptide repeat-containing protein 3, PTCD3)) were later identified (Koc et al., 2013). The overall structure of the small subunit is elongated and lends itself to be divided into 3 regions namely head, platform and foot (Fig. 1). The head region characterized by presence of *MRPS29* a GTP binding protein, the foot by *MRPS27* a pentatricopeptide repeat (PPR) domain protein (Amunts et al., 2015). MRPS27 associates with 12S rRNA and tRNA(Glu), and is required for mitochondrial translation since its knockdown causes decreased abundance in respiratory complexes and cytochrome *c* oxidase activity (Davies et al., 2012). The intersubunit bridges contacting the LSU occur along the long axis from the head to the lower body and primarily centered on the central region of the body. The ribosomes are highly dynamic with SSU displaying both ratchet like and rotational movements along its long axis (Amunts et al., 2015). The significant features of the structure include the position of the 12S rRNA which is shortened as compared to 16S rRNA in bacteria, locations of Zinc-binding proteins, *MRPS18*A, *MRPS18B*, and *MRPS18C* that were found to occupying three distinct sites, and the ability of *MRPS18C* and *MRPS18A* to coordinate the zinc atom despite missing one of the zinc-coordinating residue (Greber et al., 2015). The mRNA channel in the 28S subunit has a distinct entry (*MRPS5*, *MRPS24*, *MRPS39*) and exit regions (*MRPS37*, *MRPS28*) which are constituted by specific proteins. Structural features of the translation machinery suggest a convergent evolution with the eukaryotic ribosome since the mitoribosome has the ability to translate mRNA that lack Shine-Delgarno sequence and are leaderless. The human mitoribosome has an entrance, that is constrained such that the overall diameter is less than RNA duplex hence only single stranded mRNA could enter. At the entry site is a PPR repeat protein *MRPS39* which is postulated based on the ability of PPR domain to bind single-stranded RNA, to guide the mRNA's into the ribosomal channel. At the exit, another SSU protein *MRPS28* with a single oligonucleotide binding (OB) fold was identified to potentially interact with the mRNA due to positional conservation with bacterial bS1 protein. Unlike the bacterial protein, *MRPS28* strongly associates with ribosome through interactions with *MRPS2* and *MRPS21*(Amunts et al., 2015). The intrinsic GTPase