Regulation of human mitochondrial gene expression

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Mammalian mitochondrial DNA (mtDNA) is transcribed as precursor polycistronic transcripts containing 13 mRNAs, 2 rRNAs, punctuated by 22 tRNAs. Recently using integrated analyses we have characterized the mitochondrial transcriptome and revealed unexpected complexity of the mtDNA that includes the presence of non-coding RNAs. We have extended these analyses and using deep sequencing and functional assays we elucidate the mechanisms involved in the excision of mitochondrial tRNAs from the polycistronic transcripts that until now have remained largely unknown. We have characterized the roles of ELAC2, mitochondrial RNase P proteins 1 and 3, and pentatricopeptide repeat domain protein 1 in the processing of mitochondrial polycistronic transcripts. We used a deep sequencing approach to capture and characterize the 5′ and 3′ ends of processed mitochondrial transcripts and provide a detailed map of mitochondrial tRNA processing sites affected by these proteins. We show that MRPP1 and MRPP3 process the 5′ ends of tRNAs and the 5′ unconventional, non tRNA containing site of the CO1 transcript. By contrast, we find that ELAC2 and PTCD1 affect the 3′ end processing of tRNAs. We found that MRPP1 is essential for transcript processing, tRNA modification, translation and mitochondrial respiration. Finally, we provide the first evidence for the generation of long non-coding RNAs from the mitochondrial genome and their regulation by nuclear encoded factors.