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Letter to Editor

A tale of three RNAs in mitochondria: tRNA, tRNA derived fragments and mitomiRs

Thejaswini Venkatesh [a,*], Shaharabhanu A. Hussain [a], Padmanaban S. Suresh [b,*]

[a] Department of Biochemistry and Molecular Biology, Central University of Kerala, Kasargod, Kerala, India
[b] Department of Biosciences, Mangalore University, Mangalagangotri, Mangalore 574 199, Karnataka, India

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Dear Editor, Mammalian mitochondria is an endosymbiotic organelle that is involved in oxidative phosphorylation, apoptosis, calcium homeostasis, β oxidation of fatty acids and synthesis of heme and steroid hormones (Bienertova-Vasku et al., 2013). It consists of circular genome of 16.568 kb and encodes 13 subunits of electron transport chain (ETC) and harbors 2 rRNA and 22 tRNA genes (Gustaffson et al., 2016). Two strands (H and L) of the mitochondrial DNA replicate asynchronously and asymmetrically (Lee et al., 2008). Transcription starts at IT_{H1} and IT_{H2} for H strand and at IT_{L1} for L strand. It requires a nuclear encoded mitochondrial RNA polymerase and mitochondrial transcription factor A (mtTFA) and genes are transcribed polycistronically with tRNAs acting as punctuation marks (Lee et al., 2008). Moreover, mitochondria are semi-autonomous and require several nuclear encoded proteins for its functions. Several proteins are imported from the cytoplasm through translocases of inner and outer mitochondrial membranes. In addition to proteins, tRNAs (tRNAGln) and ribosomal RNAs (5S RNA) are imported into the mitochondria (Lee et al., 2008).

Deep sequencing experiments have revealed the presence of piRNAs (PIWI-interacting RNAs), miRNAs (microRNAs) and snoRNAs (small nucleolar RNAs) in mitochondria of HeLa and HEK293 cells (Sripada et al., 2012a). MitomiRs are miRNAs present in mitochondria. Research studies have indicated their presence in rat and murine liver, myotubes, HeLa, HEK293 cells (Sripada et al., 2012b). miR-720, miR-133b, miR-1974, miR-let7b and miR-365 localize to mitochondria in human myotubes (Barrey et al., 2011). miR-638, miR-1977, miR-7b and miR-1978 are reported to localize to mitochondria in HeLa cells (Bandiera et al., 2011). Hence, mitomiR profiles are cell type specific and they may exhibit differential regulation of mitochondrial functions. MitomiRs such as miR-15, miR-16, miR-195, miR-424, miR-338, miR-30, miR-101, miR-126 and miR-16 have been associated with mitochondrial functions for example mitochondrial metabolism, inhibition of ROS, mitochondrial dynamics, mitophagy and apoptosis (Tomasetti et al., 2014). In corroboration with mitomiRs' regulation of mitochondrial functions, few research studies have documented the presence of RNA interference components such as Argonaute 2 and Argonaute 3 in the mitochondria (Sripada et al., 2012a).

Presence of miRNAs in mitochondria raises several intriguing questions on their origin. Are they generated from mitochondrial genome? Are there any pre-miRNA or miRNA sequences present within mitochondrial DNA (mtDNA)? Barrey et al. (2011) aligned 33 pre-miRNAs and 25 mature miRNAs to human mitochondrial genome using miRBase and three of these miRNAs (pre-mir-302a, pre-let-7b and mir-365) aligned to mtDNA were shown to localize to myoblast mitochondria. However, it was not clear if these miRNAs originated from cytosol or were generated from mtDNA through a processing machinery. If a processing machinery is to work to generate mitomiRs, are RNases involved in their biogenesis? Proteome analysis has shown that DICER is not found in mitochondria (Ro et al., 2013). Additionally, there is no clear cut evidence of mitochondrial miRNA biogenesis machinery which opens up a possibility of miRNA import to mitochondria or generation of miRNAs from mitochondrial genome by simple RNase action.

Several studies have reported the import of miRNAs from cytoplasm to mitochondria. Nuclear miRNAs are associated with outer membrane of mitochondria but not in mitoplasts (Sripada et al., 2012b; Barrey et al., 2011). Entry of miRNAs into mitochondria may be mediated by mitochondrial associated proteins. PNPase (polynu-

* Corresponding authors.
E-mail addresses: thejaswinivenkatesh@cukerala.ac.in, thejaswinivenkatesh5@gmail.com (T. Venkatesh), surepadman@mangaloreuniversity.ac.in, surepadman@gmail.com, surepadman@rediffmail.com (P.S. Suresh).

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