DOI 10.18699/SBB-2022-053

mitomiRs as the common regulators of gene silencing

Vorozheykin P.[1]*, Vishnevsky O.[2], Titov I.[1, 2]
[1] *Novosibirsk State University, Novosibirsk, Russia*
[2] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*
** Pavel.Vorozheykin@gmail.com*

Key words: miRNA, mitomiR, mitochondria, evolution, targets

Motivation and Aim: To date it is well known that fundamental pathways of the miRNA biogenesis start in nucleus and end into cytoplasm. However, there is evidence that these short RNA sequences are also presented in organelles, for example in mitochondria. These observations may reveal both the nucleus miRNA translocation to the mitochondria and the existence of the miRNA maturation process within the mitochondria. The miRNA machinery proteins (Argonaute/AGO and Dicer) have been detected in mitochondria and the mitochondrial gene expression can be regulated by the miRNAs. The existence of such mitochondria associated miRNAs (the so-called mitomiRs) raises questions about their function and origin. It is still unknown, is there a specific functions of different miRNA classes according to their cell location? Are mitomiRs originally evolved or have appeared only recently? Is there a sequence or structure difference between the mitomiRs and non-mitomiRs that provides a mitomiR translocation to the mitochondria?
Methods and Algorithms: The dataset miRNA sequences were downloaded from the miRBase database (miRBase.org, release 22.1). We considered the experimental studies that demonstrate the presence of the miRNAs within mitochondria isolated from various organisms, cell types and tissue. According to these studies we construct two sets with human, mouse and rat miRNAs: mitomiRs (observed within mitochondria, 652 sequences) and non-mitomiRs (others, 4766 sequences). The homologous search was carried out by comparing Hamming distance of the aligned miRNAs and selecting those miRNA pairs that differ less than 5 % of the sequences length. To investigate the sequence and structure differences of the miRNA classes we searched for statistically overrepresented oligonucleotide motifs by ARGO-program [2]. To compare functions of the miRNAs, we explore the mitomiR and non-mitomiR targets from the experimentally validated miRNA-associated gene database miRTarBase (release 8.0) [3] and investigated the relationship of the miRNA targets with the gene ontology (GO) terms from the GeneOntology.org database (on the date 2022-03-2) [4].
Results: Comparing the miRNA homolog sequences from the miRBase we concluded that the mitomiRs are used to be more widely distributed among species (Fig. 1, A). This supports the hypothesis that mitomiRs may be recruited into mitochondria during their domestication. In addition to that, the mitomiRs are associated with a greater number of target genes than the non-mitomiRs (see Fig. 1, B), even though the less mitomiR sequences were discovered.

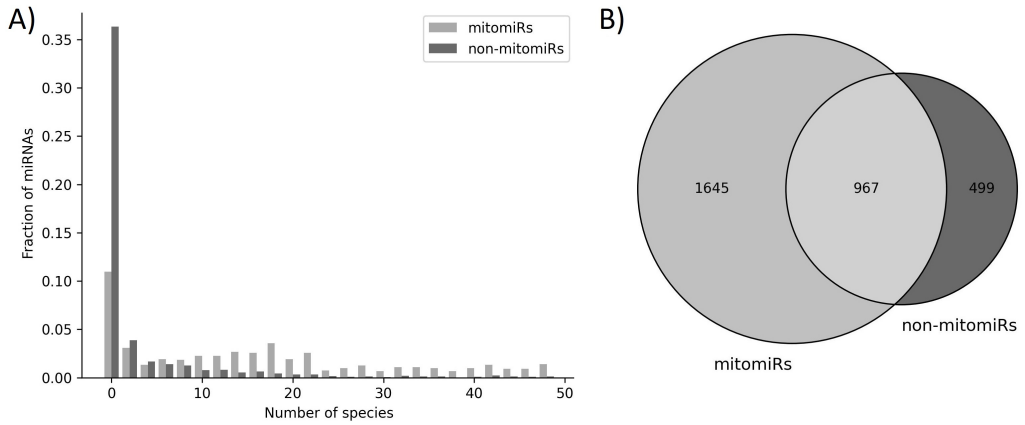

Fig. 1. A) The fraction of the miRNA sequences corresponding to the number of the species in which miRNAs have homologs; B) The number of the target genes for the mitomiRs and non-mitomiRs

Comparing the sequences of mitomiRs and non-mitomiRs we discovered several statistically overrepresented oligonucleotide motifs in mitomiRs: CAKTSHAN, KTGCANDK, HASHWSBD and others. These motifs may be signals for a specific miRNA processing (for example, a mitomiR translocation) or may directly affect the gene regulation.To explore the functions of the considered miRNAs, we performed the GO enrichment analyses for the targets lists of human mitomiRs and non-mitomiRs in three general categories “biological process”, “molecular function”, and “cellular component”. About 889 GO terms are related only to the mitomiRs targets which indicates the unique features of mitomiRs. For the common GO terms of mitomiRs and non-mitomiRs targets we calculated the Fisher’s exact test (p-value ≤ 0.05) and received 290 GO terms which are highly associated with one list of genes comparing to the other. All discovered GO terms are specifically enriched in list of non-mitomiR target genes.

Therefore, the mitomiR sequences can be identified as the common regulators while the non-mitomiRs appear to be specific ones.

Acknowledgements: The work of OV and IT was supported by the budget project No. FWNR-2022-0020.

References

1. Kozomara A., Birgaoanu M., Griffiths-Jones S. miRBase: from microRNA sequences to function. *Nucleic Acids Res.* 2019;47(D1):D155-D162.
2. Vishnevsky O., Kolchanov N. ARGO: a web system for the detection of degenerate motifs and large-scale recognition of eukaryotic promoters. *Nucleic Acids Res.* 2005;1(33):W417-W422.
3. Huang H.Y. et al. miRTarBase 2020: updates to the experimentally validated microRNA-target interaction database. *Nucleic Acids Res.* 2020;48(D1):D148-D154.
4. Ashburner et al. Gene ontology: tool for the unification of biology. *Nat Genet*. 2000;25(1):25-29.