Factors involved in mitochondrial epigenetics

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INTRODUCTION

Mitochondrion is essential for eukaryotic cells, it is needed for the correct cellular machinery. Besides nucleus, mitochondrion also has an own genome (**mtDNA**) which is regulated by many **epigenetic factors** such as methylation, TFAM content and miRNAs. A **deregulation** in those factors may result in the malfunction of key cellular mechanisms, contributing to **disease**.

OBJECTIVES: to determine the **role of mitoepigenetic mechanisms** in the control of normal mitochondrial gene expression, focusing on **miRNAs**: action, generation and methodologies based on their identification.

METHODS AND OBJECTIVES

Bibliographic search of reviews and research articles in databases such as PubMed (NCBI).
Reading and abstracting the collected literature in order to elaborate the written review.

Keywords: mitochondrial genome, mitoepigenetics, mtDNA methylation, mitomiRs.

MITOCHONDRION

1. Mitochondrial genome

Discovered in 1963 by Margit M.K. Nass-Edelson and Sylvan Nass.

16568 Kb
Light chain + Heavy chain
37 genes

Codifies for:
- 22 tRNAs
- 2 rRNAs
- 13 polypeptides (OXPHOS)

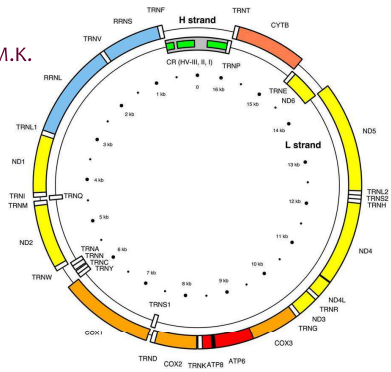

Fig. 1. Map of the Human Mitochondrial Genome.

2. Nucleus – Mitochondrion communication

Mitochondrion also needs proteins, enzymes and ncRNAs from nucleus. These are transported to mitochondrion by two main mechanisms: **TIM-TOM complex** and **PNPase** phosphorylase.

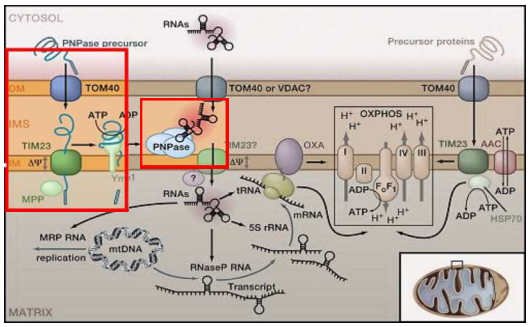

Fig. 2. Molecules' import thought TIM-TOM translocases and PNPase trimer.

MITOEPIGENETICS

Mitoepigenetics: mechanisms that change mtDNA activity not implying modifications in nucleotide sequence. How? Modifying mtDNA structure.

1. mtDNA methylation

As well as nuclear genome, mtDNA is methylated with a specific 5mC and 5hmC pattern methylation.

DNA SILENCING

Proteins founded in mitochondrion:
- ✓**mtDNMT1** (isoform of nuclear DNMT1), **DNMT3a** and **DNMT3b**
- ✓**TET1** and **TET2**.
- ✓**SAM** and its transporter **SAMC**.

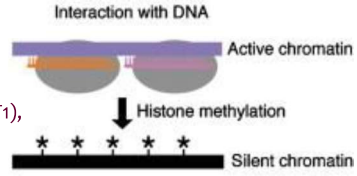

Fig. 3. Action mechanism of DNA methylation

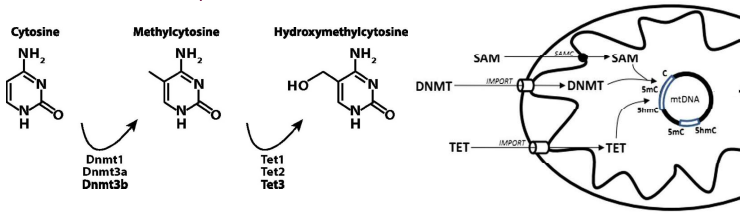

Fig. 4. Enzymes involved in mtDNA methylation and hydroxymethylation and their membrane transporters.

2. TFAM content

mtDNA has no histones. It is packed in **nucleoids** by the use of TFAM.
If TFAM bounds to mtDNA non specific regions, induces compaction.

DNA SILENCING

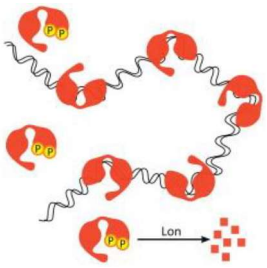

Fig. 5. TFAM induces DNA supercoil.

3. miRNAs

miRNAs in mitochondrion (**mitomiRs**) bind to complementary sequences of target mRNAs.

POSTTRANSCRIPTIONAL SILENCING

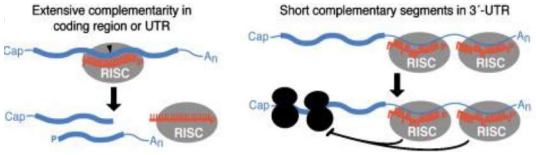

Fig. 6. mRNAs induces either transcriptional repression and/or mRNA degradation.

Biosynthesis

From nuclear genome
I. Non-canonical and/or Canonical miRNAs biogenesis.
II. Import to mitochondrion by PNPase.

From mitochondrial genome
Needed enzymes:
- **Rnases**.
- ✓ **AGO2** and/or **AGO3** (RISC components).

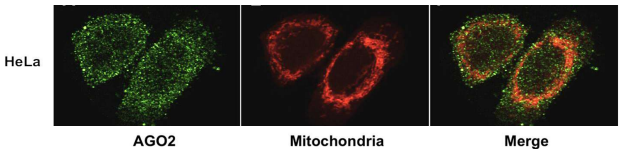

Fig. 7. AGO2 mitochondrial localization in HeLa cell line.

mitomiRs may come also from short RNA fragments of tRNAs: **tRFs** and **tsRNAs** considering that them align significantly with mitochondrial tRNAs.

Associated methodologies

Aim: identify mitomiRs

Method	miRNAs and pre-miRNAs
***In situ* hibridation**	(hsa-miR) - 494, 1275, 1974, miR-let-7b, miR-365, pre-miR-302a and pre-let7b.
q-PCR	miR-1.
Northern Blot	mmu-mitosR-L-A_3, mmu-mitosR-L-P + _6, mmu-mitosR-HA_1 and mmu-mitosR-HP_3.
Microarrays	hsa-miR-181c, (miR) - 328, 494, 513, 638, (mmu-miR) -142-3p, 142-5p, 146a, 155, 223, 122, 134, 155, 202-5p, 223 and 494.

Aim: identify miRNAs transcripts from mtDNA

Tables 1-2. founded miRNAs by different methodologies.

Method	miRNAs and pre-miRNAs
Alignment	(mir) - 365, 31, pre-let-7b, (pre-mir) - 302a, 1267 and 1296.
Deep sequencing	(hsa-miR-let) - 7b, 7g, (hsa-miR) - 107, 181a, 221, 320a, 16, 103 and 146a.

Mitochondrial dysfunction

Mutations → miRNA deregulation → Mitochondrial dysfunction → **Diseases**

CONCLUSIONS

- Mitochondrion is one of the most important organelles in cell.
- Mitoepigenetic factors regulate mtDNA in a different way, usually **inhibiting gene expression**.
- A deregulation in those mechanisms may cause a **metabolic disorders, cardiovascular diseases** or **cancer**.
- Those mitomiRs that regulate mtDNA, but are transcribed from nuclear genome, might have their **origin in mitochondrial genome**.

REFERENCES:
[1]. Sierra-Delgado J.A., C.-G. G. A. (2016). MECHANISMS FOR THE EPIGENETIC REGULATION OF MITOCHONDRIAL DNA, XXVII (December), 7–15.
[2]. Venkatesh, T., Hussain, S. A., & Suresh, P. S. (2017). A tale of three RNAs in mitochondria: tRNA, tRNA derived fragments and mitomiRs. Journal of Theoretical Biology, 435, 42–49. https://doi.org/10.1016/j.jtbi.2017.09.002
[3]. Borralho, P. M., Rodrigues, C. M. P., & Steer, C. J. (2015). microRNAs in Mitochondria: An Unexplored Niche. microRNA: Basic Science, 31-51. https://doi.org/10.1007/978-3-319-22380-3
[4]. Sripada, L., Tomar, D., & Singh, R. (2012). Mitochondria: One of the destinations of miRNAs. Mitochondrion, 12(6), 593–599. https://doi.org/10.1016/j.mito.2012.10.009