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Noncoding RNAs regulatory network in mitochondria

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Introduction

Mitochondria are powerhouses of eukaryotic cells and possess own bioenergetically specialized genetic system also known as mitochondrial DNA (mtDNA). In human cells, mtDNA encodes 22 transfer RNAs, 2 ribosomal RNAs and 13 proteins which are subunits of the oxidative phosphorylation machinery. Due to the small size of the mitochondrial genome, mitochondrial biogenesis and function are largely dependent on a number of nuclear-encoded molecules that are imported to mitochondria via the translocase of the outer mitochondrial membrane complex. In line with that, the mitochondrial proteome and transcriptome landscape represents an intricate mixture of intrinsic (i.e. mitochondrial) and extrinsic (i.e. nuclear-encoded) molecules. Thus, mitochondrial metabolism, as well as cellular homeostasis, require coordination of expression of two genomes and well-tuned cross-talk between the nucleus and mitochondria [Figure 1].

Although significant progress has been achieved in elucidating the molecular mechanisms of mito-nuclear communication, the regulatory network of this communication remains to be fully explored. Mitochondria are able to import various RNAs from the cytosol and also export particular RNAs. An increasing body of data from genome-wide analyses and RNA sequencing experiments has revealed that a large part of the human genome is transcribed into RNA molecules that are unable to encode proteins, the so-called noncoding RNAs (ncRNAs). Arbitrarily, ncRNAs are classified into small ncRNAs, which are up to 200 nucleotides long, and long ncRNAs RNAs (lncRNAs), which are longer than 200 nucleotides. Small RNAs contain, the well-known microRNAs (miRNAs) which down-regulate the expression of target messenger RNAs through base pairing. LncRNAs regulate gene expression mostly at the epigenetic level. According to the last GENCODE release (v30), the human genome contains 7576 small and 16193 long noncoding RNA genes. Accumulating evidence indicates that ncRNAs may contribute to the synchronization of essential cellular and mitochondrial biological pathways, acting as "messengers" between the mitochondria and the nucleus [1].

Mitochondrial miRNAs

MicroRNAs (miRNAs) are small endogenous and ubiquitous 18 – 25 nucleotide long ncRNAs. MiRNAs are master regulators and fine-tuners of gene expression [2]. Studies in different species have reported that pre-miRNAs, as well as mature miRNAs, are present in the mitochondria [3]. Although mitochondrial miRNAs are almost entirely transcribed from nuclear genes involved in mitochondrial function or the expression of mitochondrial genes, due to their localization in the mitochondria, some miRNAs are named as MitomiRs. Accordingly, they are involved in main mitochondrial pathways: oxidative phosphorylation, electron transport chain components and lipid metabolism.

MiR-15b, miR-16, miR-195, and miR-424 have emerged as regulators of oxidative phosphorylation, miR-183 and miR-743a regulate several steps in Krebs cycle, and miR-181c, miR-210 and miR-338 target mitochondrial electron transport chain components [4].

Several miRNAs have been identified as key players in lipid metabolism. MiR-33 has been recognized as an important regulator of cholesterol levels, miR-24 and miR-143 are connected to lipid metabolism, and miR-24 and miR-126 have been associated with fatty acid metabolism [4]. In adipocytes, miRNAs are involved in different levels of regulation of mitochondrial function such as: fission (miR-27a/b, miR-761, miR-484, and miR-30 family), fusion (miR-26a; miR-140), apoptosis (miR-15a, miR-143 and miR-30 family), mitophagy (miR-181a and miR-137), thermogenesis (miR-30b/c, miR-26a, miR-196a, miR-182, miR-203, miR-378, miR-382, miR-455, miR-34a, miR-93, miR-106b, miR-125b-5p, miR-133, miR-155, and miR-7i-5p), and reactive oxygen species production/inflammation (miR-21, miR-27a/b, miR-132, miR-155, miR-183, miR-221, miR-872 and miR-223) [5]. Expression profiles of mitochondrial miRNAs differ between various cell types and further studies are needed to explore miRNAs landscape in mitochondria of different type of healthy and diseased tissues.

Mitochondrial lncRNAs

Deep-sequencing analysis has revealed several lncRNAs involved in the regulation of mitochondrial function, generated from the nuclear or mitochondrial genome. Three lncRNAs, lncND5, lncND6, and lncCyt b RNA have been discovered within the mitochondrial transcriptome and they may contribute to the regulation of mitochondrial gene expression [6]. The nuclear DNA-encoded lncRNA RMRP is critical for mtDNA replication and RNA processing [6]. A very small amount of RMRP might even be sufficient to promote an RNase MRP activity.

The lncRNAs called SncmtRNA and ASncmtRNAs are present in both mitochondria and the nucleus, supporting a potential role in mito-nuclear communication and retrograde signaling [6].

The lncRNA SAMMSON predominantly localizes to the cytoplasm of human melanoblasts and melanoma cells and interacts with the master regulator of mitochondrial homeostasis and metabolism p32. Knockdown of SAMMSON in melanoma cells decreased mitochondrial targeting of p32 and caused mitochondrial protein synthesis defects, which ultimately triggered apoptotic cell death [7].

The mtDNA-encoded lncRNA named LIPCAR, a chimeric/fusion transcript formed between the 5’-end of COX2 gene and 3’-end of CYTB, was regulated in plasma samples

from patients developing heart failure after acute myocardial infarction and was shown to predict survival [8].

Conclusions

Growing evidence highlights ncRNAs as important players in the regulation of nuclear and mitochondrial gene expression. Thus mitochondrial dysfunction caused by disruption of mitochondrial-nuclear communication may participate to the development of several diseases such as cardiovascular diseases, diabetes, cancer and neurological diseases. Search for key players of mitochondrial ncRNAs regulatory network may catalyse the identification and development of novel diagnostic and therapeutic approaches of mitochondrial dysfunction-related diseases.

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Figures

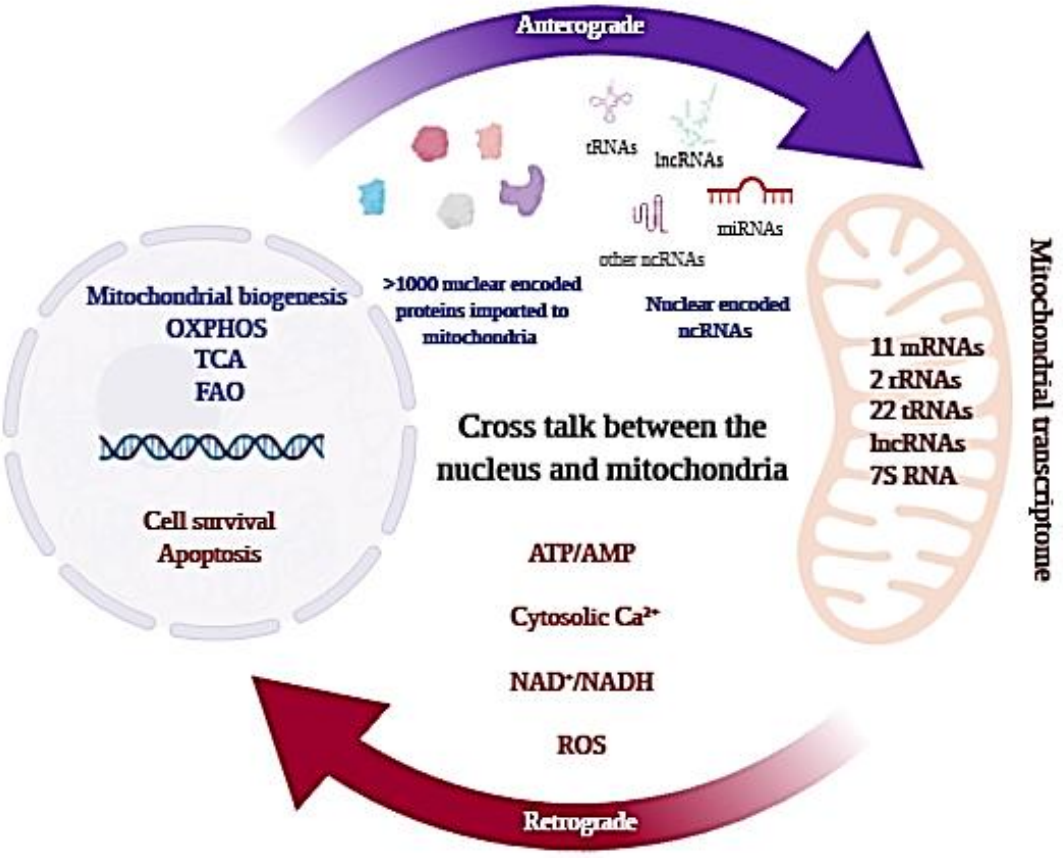

Figure 1. A dialog between the nucleus and mitochondria. FAO, fatty acid oxidation; lncRNAs, long noncoding RNAs; miRNAs, micro RNAs; ncRNAs, noncoding RNAs; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid.