Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 5 Issue 12 December 2021

Review Article

RNA Processing and Degradation in Eukaryotic Cells' Mitochondria

Vahideh Hamidi Sofiani[1], Arefeh Ebrahimian Shiadeh[1], Mohammadreza Kalani[2] and Abdolvahab Moradi[1]*

[1]Department of Microbiology, Golestan University of Medical Sciences, Gorgan, Iran

[2]Department of Molecular Medicine, Golestan University of Medical Sciences, Golestan, Iran

***Corresponding Author:** Abdolvahab Moradi, Department of Microbiology, Golestan University of Medical Sciences, Gorgan, Iran.

Received: September 12, 2021

Published: November 16, 2021

Abstract

The mammalian mitochondrial genome can encode tRNAs, rRNAs, and mRNA. Moreover, the mitochondrion is an important site for RNA degradation phenomenon in addition to transcriptional duties, however, there are different assumptions related to this phenomenon. It has been suggested that the presence of RNA granules along with a variety of enzymes in the mitochondria may be involved in the RNA degradation process. In this paper, we try to investigate the factors affecting RNA degradation in mitochondria.

Keywords: Mitochondria; RNA; mRNA

Introduction

The human mitochondrial genome is much smaller than the nuclear genome; however, transcription and translation of mitochondrial genes are essential for cell prosperity [1]. The organization of the mitochondrial DNA (mtDNA) is very similar to bacterial DNA because the mitochondria originate from bacteria. Like bacteria, the mtDNA is located within protein-DNA complexes distributed throughout the mitochondria, which are called nucleoid structures [2]. Each mitochondrion has more than hundreds of nucleoids and each nucleoid may include more than one mtDNA. Each nucleoid can be considered as a separate genetic unit. 0.1 - 2% of the total DNA in most mammalian cells belongs to Mitochondrial DNA. mtDNA has several unique characteristics like circular form, its length, 16 kbp, and its maternal inheritance. Two rRNAs, 22 tRNAs, and 13 proteins, all of which are involved in the oxidative phosphorylation process encode by mtDNA [3]. Because mtDNA is organized within nucleoid structures, it lacks histones [4]. Five to seven mtDNA molecules can be located in the space of an average nucleotide nucleus of 70 nm [4]. Here we summarize the current knowledge on the factors affecting RNA degradation in human mitochondria.

The transcription process

The mtDNA has two different strands: the heavy strand and the light strand. The majority of coding areas on the heavy and light strands are only involved in encoding the MT-ND6 (NADH-ubiquinone oxidoreductase chain 6) protein and eight tRNAs. Transcription of both strands takes place at the same time and leads to the formation of a long transcript which is then processed. The mtDNA transcription is done by enzymatic machinery that is different from the nuclear system and contains: the DNA-directed RNA polymerase (POLMRT) [5], the mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M) [6,7], the mitochondrial transcription factor A (TFAM) [8,9], the mitochondrial transcription elongator factor (TEFM), a single strand binding protein (SSBP), and the family of mitochondrial transcription termination factors (mTERF1 - 4). The process in the elongation phase requires

a complex set of several factors including MRPL12 (39S ribosomal protein L12), POLMRT, and TEFM [8,10,11]. Moreover, from formation to the decomposition phase, mtRNAs must mature to be able to produce the mtDNA-encoded proteins. Therefore, the basic stages of mitochondrial gene expression are an adaptation to the cellular metabolic needs. Somehow, the processing and maturation of mitochondrial RNA (mtRNA) is the responsibility of a protein structure called mitochondrial RNA granules (MRGs). Which regulates post-transcriptional processing and allows all mtRNAs to fully mature before protein synthesis [12,13]. There is a hypothesis that MRGs are not only sites of RNA processing, but also the site of RNA degradation because they contain mtRNA Destructive proteins such as hSUV3 (ATP-dependent RNA helicase SUPV3L1) and PNPase. Therefore, they are also called "mitochondrial degradosomes" [14]. Furthermore, the primary polycistronic transcript undergoes post-transcriptional processing by a large number of proteins such as Mitochondrial ribonuclease P protein (MRPP), and RNA-modifying enzymes. From RNA-modifying enzymes we may mention the TFB1M (Dimethyladenosine transferase 1), PTCD3 (Pentatricopeptide Repeat Domain 3), and the mitochondrial poly-A polymerase. The mitochondrial translation machinery proteins include structural proteins of the small (mt-SSU) and large (mt-LSU) mitochondrial ribosomal subunits, aminoacyl tRNA synthetases, and factors involved in ribosome assembly and disassembly. MRGs also have an important role in mitochondrial ribosome synthesis and mitochondrial translation regulation [15,16]. A greater degree of temporal regulation of both mtDNA and its transcription products processing takes place within non-membrane bound compartments. mtRNA at the end of her life inhabits in specific foci, called D-foci (degradation foci). D-foci are mostly composed of the mitochondrial degradosome [14,16]. D-foci and MRGs co-localize together, however, it is not clear whether these foci are a subset of MRGs or have separate compounds. several catalytic mitochondrial enzymes and other mitochondrial and non-mitochondrial proteins are located in this region. mtDNA is transcribed to two polycistronic transcripts that must be processed to be formed several RNAs [17]. The mt-tRNAs sequences are located between mt-rRNAs or mt-mRNAs sequences. According to the accepted mt-tRNA punctuation model [18] cleavage of the mt-tRNA sequences is required to release the mt-rRNAs or mt-mRNAs. There are some exceptions in flanking of mRNAs by mt-tRNAs, like for ATP6/8 and COIII or ND5 and CytB. Researchers suggest that the early stages of mitochondrial transcription can be done inside the mitochondrial RNA granules because most of the proteins involved in mtRNA processing are located in these granules [19-21]. In the granules that participate in the 5` - end of the mt-tRNAs processing, an RNase P protein complex is found that is composed of MRPP1, 2, and 3 [20,22].

In the MRGs, both strands of mtDNA are capable to transcribe two polycistronic mtRNA molecules that are processed to be formed three different RNAs like tRNA, rRNA, and mRNA [1]. Then these RNAs are more processed to their mature form as mitochondrial polypeptides. Subsequently, damaged mtRNA must be degraded to avoid the formation of an improper transcript. Moreover, when the mRNA, tRNA, and rRNA molecules are frequently translated to proteins, they might be degraded to eliminate improper or damaged transcripts. Likewise, in addition to the presence of destructive complexes in the cytoplasm or nucleus which are responsible for RNA degradation, there are destructive agents in mitochondria. So, realizing of RNA degradation process in mitochondria could be considered as the main part of biological events in the body.

Mystery of RNA degradation in mitochondria

Initially, the site of mitochondrial transcript degradation was known to be in the mitochondrial matrix, but it is now believed that transcript degradation may occur in the mitochondrial interstitial space. The counterpart of polynucleotide phosphorylase (PNPase) in humans as a complex as hSUV3/PNPase is the best-characterized protein complex dedicated to the mt-mRNA degradation in the mitochondrial matrix [14]. PNPase is a conserved phosphorolytic 3′-5′ processive exoribonuclease that is seen in all of the phyla such as humans [23]. PNPase complexes with the hSuv3p helicase form the mitochondrial exosome as the mitochondrial degradosome [14]. The mitochondrial degradosome formation takes place in a region, termed D-foci, that are specialized centers for RNA degradation. In addition to containing degradosomes, D-foci is also localized to newly synthesized mtRNA, so a subset of MRGs may participate in the RNA degradation process. hSUV3 is an NTP-dependent helicase with the ability to unwind different DNA and RNA. In addition, it is involved in the degradation of the damaged mtRNAs and plays a key role in the decay of the properly processed RNA molecules [24]. In this process, PNPase has a 3'- 5' phosphorolysis and 5'- 3' RNA polymerization function, that helps hSUV3 in RNA degradation [25,26]. Also, PNPase participates in several processes in RNA metabolism and is detectable in several locations in the cell, including the mitochondrial matrix and the mitochondrial intermembrane

space [27]. It participates in the degradation process of RNA and the polyadenylation process in the mitochondrial matrix, while it is involved in the entry of different RNAs from the cytoplasm into the intermembrane space. PNPase has also been proven to destruct the non-coding antisense RNAs produced by the transcription process through interaction with G-rich sequence factor 1 (GRSF1) [28]. This protein binds RNAs transcribed from three adjacent genes on the light strand of mtDNA, including the ND6 mRNA and the long noncoding RNAs for cytb and ND5. These bindings have a significant effect on mitochondrial RNA stability, abnormal loading of mRNAs and lncRNAs on the mitochondrial [29]. REXO2 is another exoribonuclease that presents in both intermembrane space and the mitochondrial matrix and has a very important 3'- 5' exonuclease activity and can degrade oligonucleotides in the matrix. Till now, studies on REXO2 were limited to its ability to degrade small single-stranded RNA and DNA fragments *in vitro.* This enzyme can localize in cytosolic and mitochondrial fractions. likewise, the mitochondria have a dual localization form in both the intermembrane space and the matrix. Deletion of this protein by RNA interference affects the morphological phenotype of human cells. Moreover, deficiency of REXO2 impaired de novo mitochondrial protein synthesis and decrease mitochondrial nucleic acid content [24]. Another protein that is involved in RNA degradation is leucine-rich pentatricopeptide repeat (PPR) containing protein (LRPPRC). It is associated with RNA and is mainly present in the mitochondrial matrix. It can inhibit the PNPase-mediated RNA degradation by inducing the mitochondrial poly(A) polymerase (mtPAP) to promote polyadenylation [30]. Stem-loop-interacting RNA binding protein (SLIRP) is another protein that with LRPPRC as LRPPRC/SLIRP complex prevents the degradation of mtRNAs [31]. So LRPPRC can protect a pool of translationally inactive mtRNAs that are not associated with the ribosome. Moreover, LRPPRC/SLIRP complex consider as a suppressor for PNPase/hSUV3 activity. During the investigation of ribonucleases, a key enzyme in mtRNA degradation, an unknown protein from the Metallo-β-lactamase (MBL) superfamily was identified as Lactamase beta 2(LACTB2). Unlike other mitochondrial proteins, such as GRSF1 [1] and RNase P [33] or PNPase and hSuv3, that form protein complexes, LACTB2 is not as complex. This protein is soluble, monomeric, and human mitochondrial matrix protein that has endoribonucleolytic activity on ssRNA especially after purine-pyrimidine sequences. Generally, LACTB2 is a key factor in the turnover of mitochondrial RNA and is necessary for mitochondrial performance in human cells [32].

Figure 1

Conclusion

In a conclusion, although mitochondria include the smallest portion of the cellular genetic material, however, considered important organelles in-process and degradation of RNA transcripts. The degradation of RNA plays a critical role in RNA metabolism and gene expression. There is an extensive RNA degradation network in eukaryotic cells including the mitochondrial RNA degradation (MRD) site. The MRD sites are responsible for the protection of the cell from dangerous nonfunctional RNA molecules. Despite the small dimensions, this organelle is an undeniable factor in eukaryotic cell's RNA stability. deficiency of this degradation network may lead to critical conditions for the body systems.

Acknowledgements

Not applicable.

Declaration

This study has been conducted in Microbiology Department of the School of Medicine Golestan University of Medical Sciences.

Authors' Contributions

A.E and V.H designed the study. All authors read and approved the final version of the manuscript.

Funding

No funding.

Availability of Data and Materials

Please contact author for data requests.

Ethics Approval and Consent to Participate

This study was approved by the Golestan University of Medical Sciences".

Consent for Publication

Not applicable.

Competing Interests

The authors declare no conflicts of interests.

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