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Review article

Role of microRNA in the regulation of mitochondrial functions

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Abstract
Mitochondria supply eukaryotic cells with energy and perform other essential cellular functions. Mitochondrial functions are regulated by the products of both nuclear and mitochondrial genomes, which include micro (mi)RNAs, 18- to 24-nucleotide non-coding RNAs that provide post-transcriptional inhibition of target gene expression. Recent studies have shown that miRNAs are expressed in mitochondria and regulate mitochondrial energy metabolism, apoptosis, and biogenesis. This review discusses the expression of miRNA in mitochondria and the role of miRNAs in the regulation of mitochondrial functions including regulation of mitochondrial metabolism, apoptosis pathway, dynamic equilibrium and autophagy. This review also addresses the role of miRNAs in cancer detection and treatment. The overview of the current state of knowledge regarding the role of miRNAs in mitochondria will provide basis for the future research.
Keywords: Mitochondria, miRNAs, mitochondrial equilibrium, metabolism.

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Introduction

Mitochondria provide the cell with energy, and also participate in oxidative phosphorylation reactions, regulate intracellular calcium balance, act as a trigger for apoptosis, and modulate other basic cellular processes [1, 2]. Mitochondrial function is regulated by the products of both nuclear and mitochondrial genomes. The latter encodes 37 genes, two ribosomal (r)RNAs, 22 transfer (t)RNAs, and 13 mitochondrial oxidative phosphorylation complex subunits. Most mitochondrial proteins (~98%) including those involved in mitochondrial DNA replication, transcription, translation, are encoded by nuclear genes and transported to mitochondria.

Micro (mi)RNAs are conserved, 18- to 24-nucleotide (nt) non-coding RNAs with temporally and spatially restricted expression patterns that bind to specific sites in the 3' untranslated region (UTR) of mRNAs, thereby targeting them for degradation or inhibiting their translation and thus providing negative regulation of target gene expression at the post-transcriptional level [3, 4]. MiRNAs regulate cell proliferation, differentiation, apoptosis, fat metabolism, and oxidative stress, and are implicated in normal physiological processes as well as human diseases. Recent studies have shown that miRNAs are expressed in mitochondria and regulate mitochondrial energy metabolism, apoptosis, and biogenesis [5–7].

miRNA expression in mitochondria

The miRNAs are encoded by nuclear DNA and are cut into small fragments in the cytoplasm before being transported to mitochondria by an unknown mechanism. A microarray analysis of highly purified mitochondria showed enrichment of specific miRNAs [5]. The number of miRNA-specific mitochondria varies by tissue and cell type; for instance, the adult mouse liver expresses 15 mitochondrial miRNAs, including miR-122, -805, and -609 [6], whereas mitochondria in human muscle cells contain more than 20 miRNAs [8]. HeLa cells express 13 miRNAs, of which three have miR-1947, -177, and -1978, target the mitochondrial tRNA genes *TRNE* and *TRNN* and the rRNA gene *RNR1* [9]. We have previously shown that the renal cortex of a normal mouse expresses several mitochondrial miRNAs that were present in the lumen at the concentrations > 50-fold higher or, in other cases, 30-fold lower than in the cytoplasm. *In situ* hybridization experiments have shown that pre-mir-302a and pre-let-7b expressed in mitochondria are encoded by the mitochondrial genome [10]. A group of miRNAs known as myo-miRNAs, miR-181a, -16-1, -133a, -181b, and -206 were found to promote muscle cell proliferation [11, 12], although those are encoded by the nuclear rather than the mitochondrial genome [9].

In addition to miRNAs, key components of miRNA regulation are present in mitochondria. MiRNA regulation of target gene expression is achieved by complementary binding of target mRNAs with the RNA-induced silencing complex, of which the key component Argonaute (Ago)2 [13] is present in mitochondria [6, 9]. MiR-181c, which is encoded by the nuclear genome, regulates the expression of the mitochondrial gene *mt-cytochrome C oxidase* (*COX*)*I* and thereby modulates energy

metabolism. Berray et al. identified potential target loci for 169 miRNAs in the mitochondrial genome; for instance, NADH dehydrogenase (*ND*)*1*, *4*, *4L*, and *6*, *cytochrome B*, and *COX1* each have dozens of miRNA-binding sites, whereas *let-7b* targets ATP synthase F0 subunits 6 and 8, COX2, and ND5 [14], substantiating the "many-to-one and one-to-many" rule of miRNA-mRNA interaction [8]

A link between miRNAs and mitochondrial dysfunction has been established in animal models. For example, in a mouse model of streptozotocin-induced type I diabetes mellitus, which is associated with mitochondrial dysfunction, the expression of the miRNAs miR-494, -202-5p, -134, and -155 in hepatic mitochondria was significantly upregulated while that of miR-705 and -122 was reduced with respect to healthy control mice. Yuan et al. in a study found that aldosterone-induced kidney damage in mice occurs simultaneously with mitochondrial dysfunction and is accompanied by a significant change (up- or down regulation) of renal cortex mitochondrial miRNA [15]. These lines of evidence implicate miRNAs in mitochondrial dysfunction, although the detailed mechanisms remain to be elucidated.

miRNA regulation of mitochondrial metabolism

Mitochondria are the main site of oxidative metabolism of sugars, fats, and amino acids in eukaryotic cells, and provide energy for the cell by generating ATP through oxidative phosphorylation reactions. The majority of mitochondrial proteins is encoded by the nuclear genome [16]. COXIV is a component of mitochondrial respiratory chain that is encoded by nuclear DNA and is involved in the mitochondrial synthesis of ATP; changes in COXIV expression level can therefore affect mitochondrial function. It has been reported that miR-338, a neuron-specific miRNA, can bind the 3' UTR of the *COXIV* gene and inhibit expression of the mRNA and protein; therefore, suppressing the endogenous expression of miRNA-338 improves mitochondrial oxygen consumption and activity and ATP production [17].

In mitochondria, glutamine is converted to glutamic acid, which then enters the Kreb's cycle. MiR-23a and -23b inhibit mitochondrial function by suppressing glutaminase expression [18]. Other studies have shown that MDA-MB231, MCF7, HT29, and HCT116 human tumor cells express high levels of miR-210 under hypoxic conditions [19], and that miR-210 inhibition of iron-sulfur enzyme cluster expression blocks the mitochondrial respiratory chain [20].

Some miRNAs regulate the expression, biosynthesis, and secretion of insulin [21]. In mouse pancreatic β-cells, miR-15a inhibits the expression of endogenous uncoupling protein 2, an inner mitochondrial membrane transport protein that promotes the synthesis of insulin and can uncouple electron transport and phosphorylation, thereby impeding ATP production [22]. Insulin resistance can lead to mitochondrial dysfunction, although the underlying mechanisms are poorly understood [23]. It was recently reported that miR-126 targets insulin receptor substrate-1 to alter insulin resistance. These findings indicate that miRNAs should be explored as potential therapeutic agents in the treatment of diabetes mellitus.

MiR-696 regulates fatty acids metabolism and mitochondrial biogenesis by targeting peroxisome proliferator-activated receptor-gamma co-activator 1-α [10], which promotes aerobic metabolism and mitochondrial function in skeletal muscle. When overexpressed, miR-696 inhibits fatty acid oxidation and reduces mitochondrial DNA copy number, whereas inhibiting miR-696 has the opposite effect [10, 24].

Role of miRNAs in the mitochondrial apoptosis pathway

Apoptosis is a tightly regulated process of cell death that plays an important role in cell growth, development, and differentiation as well as in pathological states. Apoptosis is triggered by extrinsic and intrinsic factors; the former involves tumor necrosis factor α and the binding of Fas ligand to its receptor, which is mediated by Fas-associated death domain proteins. This leads to the accumulation of procaspase-8 in the cytoplasm and the formation of the death-inducing signaling complex [25]. The intrinsic or mitochondrial apoptotic pathway involves DNA damage-induced activation of tumor suppressor genes such as *p53*, which in turn stimulates the expression of pro-apoptotic molecules of the B cell lymphoma (Bcl)-2 family, such as Bcl-2-associated X protein and Bcl-2-associated death promoter, thereby inducing the release of pro-apoptotic molecules [26] such as cytochrome C [27] and second mitochondria-derived activator of caspase and direct IAP-binding protein with low PI, also known as Smac and DIABLO, respectively [28]. Cytochrome c, cytoplasmic apoptotic protease-activating factor 1, and procaspase-9, mediate apoptosis by activating

caspase-9 which, along with caspase-8 induces apoptosis.

MiR-15a and -16-1 regulate the mitochondrial apoptotic pathway by activating oncogenes such as Bcl-2 and myeloid cell leukemia 1 and inducing cytochrome c release from mitochondria, thereby disrupting mitochondrial membrane stability and function [29]. Under normal circumstances, miR-143 is specifically expressed by colon cells, but the level is reduced in colon cancer patients. MiR-143 targets extracellular signal-regulate kinase 5 [30] to modulate mitochondrial function and trigger apoptosis [31]. The miR-1 is expressed in skeletal muscle cells; when overexpressed, it triggers the release of cytochrome c and undermines mitochondrial membrane stability, leading to apoptosis [32].

miRNA regulation of mitochondrial dynamic equilibrium

Mitochondrial biogenesis comprising fusion and fission is a dynamic process that occurs throughout the life cycle of a cell, ensuring the stability of mitochondrial structure and function [33]. Biogenesis involves mitochondrial DNA replication and an increase in mitochondrial matrix volume; however, mitochondrial DNA is not replicated during the fission process, which ultimately generates small mitochondria that later mature [33, 34]. Mitochondrial fusion and fission inhibit and trigger apoptosis, respectively [35], while excessive fission is implicated in diseases such as diabetic nephropathy and brain and skeletal muscle disorders [36–38].

The miRNAs also regulate mitochondrial structure. For instance, stimulating myocardial cells with hydrogen peroxide reduces the expression of three members of the miR-30 family, miR-30a, -30b, and -30d that are highly expressed in the heart. Dynamin-related protein (DRP)1 plays a key role in mitochondrial fission, specifically in the fragmentation of the mitochondrial outer membrane; *p53*, a target gene of the miR-30 family, promotes *Drp1* transcription while triggering apoptosis. Mitochondrial fission and apoptosis are thus regulated via targeting of P53 and DRP1 by miR-30 members [39]. The miR-499, which is encoded in an intron of the myosin gene, is enriched in myocardial cells and inhibits apoptosis via the calcineurin/Drp1 signaling pathway [40, 41]. Some studies have reported the regulation of miR-499 transcription by P53 [42], while *Drp1* regulation by miRNAs affects mitochondrial dynamics and apoptosis. The underlying mechanisms are complex, but may involve the fission 1 protein [43]. Additional studies are required to clarify the regulation of mitochondrial dynamics by miRNAs.

miRNAs in mitochondrial autophagy

Autophagy is the lysosome-mediated degradation of intracellular proteins and organelles involving changes to cell membrane structure [44, 45]. This dynamic process balances cellular anabolism and catabolism, thereby stabilizing the intracellular environment and promoting cell survival. Autophagy can be triggered by cell starvation, absence of growth factors, hypoxia, and a variety of pathological conditions. During autophagy, cellular organelles and other components are packed within a phagosome that is transported via microtubules to fuse with the lysosome, leading to substrate degradation. Mitochondrial autophagy or mitophagy is a process by which the cell removes damaged mitochondria and maintains homeostasis [46]; this regulates mitochondrial number so that the biological and metabolic demands of the cell can be balanced [47]. During mitochondrial membrane depolarization in mammalian cells, phosphatase and tensin homolog (PTEN)-induced putative kinase (PINK)1 triggers the transport of Parkin proteins from the cytoplasm to mitochondria and the subsequent ubiquitination of mitochondrial proteins, leading to the formation of autophagosomes containing damaged mitochondria [48].

MiR-101, -204, and -30a regulate autophagy by targeting autophagy-related proteins [49–51]. Regulation by miR-34b/c is thought to be an early factor in Parkinson's disease, although whether it involves mitochondrial dysfunction has yet to be established [52]. The up-regulation of miR-21 expression in many types of human tumors and the regulation of PTEN expression by miR-21 has been demonstrated [53, 54]. PTEN in turn regulates PINK-1, although further study is required to determine how this controls the mitophagy pathway.

Role of miRNAs in cancer

The Warburg effect postulates that cancer cells use glycolysis instead of oxidative phosphorylation to generate ATP, even in the presence of oxygen [55, 56]; this enables tumor cells to sustain their rapid growth, which involves many factors including miRNAs [57]. It has been proposed that miRNAs can serve as a tool in tumor detection and treatment [58]. For example, miR-200a was found to reduce the growth of tumors in liver [59] and breast [60]

cancers. Many miR-200a target genes have been identified [61, 62], including mitochondrial transcription factor A (TFAM), a major transcription factor in mitochondria [63]. Changes in TFAM expression have been linked to tumor progression and the development of chemoresistance [64]; this may be due to miRNA regulation, since overexpressing miR-200a inhibits TFAM level [60].

The failure of apoptosis is considered as a major cause of therapeutic resistance in several cancers, including non-small cell lung cancer [65]. This program is controlled by many factors, including the activation of P53 as part of the DNA damage response. P53 stimulates the transcription of genes containing P53 binding sites. The miRNAs maintain cellular functions that are dysregulated in cancer cells, such as proliferation, differentiation, and apoptosis [66-68]. Given that they are directly activated by P53 [69], miR-34 family members play a crucial role in tumor suppression, possibly through modulation of mitophagy [69].

The miR-126 acts as a tumor suppressor in many types of human cancer, including oral squamous cell cancer (OSCC), bladder, lung and colorectal cancers [70-73]. In OSCC cells, the miR-126 expression is significantly lower than in adjacent normal tissues [70]. The miR-126 and acts as a tumor suppressor in malignant mesothelioma (MM), and also regulates mitochondrial function by modulating energy production and respiration and increasing glycolysis in MM cells. These findings provide evidence of the key role of miRNAs in cancer, and suggest that miRNAs can serve as tumor biomarkers and as agents or targets for cancer treatment.

Summary

Mitochondria are essential organelles in eukaryotic cells that provide energy to the cell and also play an important role in apoptosis and other cellular processes. The mitochondrial dysfunction is the basis of many diseases. miRNAs mediate post-transcriptional gene regulation and thereby regulate mitochondrial metabolism, the mitochondrial apoptotic pathway, and mitophagy. The discovery of mitochondria-specific miRNAs underscores the interaction between the nuclear and mitochondrial genomes in the regulation of miRNA expression and presents new avenues for studying the regulation of mitochondrial function. Moreover, research on mitochondrial dysfunction and the role of miRNAs can provide new insight into the pathogenic mechanism of diseases such as cancer as well as potential treatment strategies.

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