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Control of mitochondrial activity by miRNAs

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Abstract

Mitochondria supply energy for physiological function and they participate in the regulation of other cellular events including apoptosis, calcium homeostasis and production of reactive oxygen species. Thus, mitochondria play a critical role in the cells. However, dysfunction of mitochondria is related to a variety of pathological processes and diseases. MicroRNAs (miRNAs) are a class of small noncoding RNAs about 22 nucleotides long, and they can bind to the 3′ un-translated region (3′UTR) of mRNAs, thereby inhibiting mRNA translation or promoting mRNA degradation. We summarize the molecular regulation of mitochondrial metabolism, structure and function by miRNAs. Modulation of miRNAs levels may provide a new therapeutic approach for the treatment of mitochondria-related diseases.

Mitochondria

Mitochondria are main oxidative phosphorylation reaction and energy production organelles, and they supply energy for cellular physiological functions. Besides supplying energy, mitochondria participate in other cellular events. One of the well known cellular roles of mitochondria is their involvement in the complex apoptotic signaling pathways [Lee et al., 2004; Suen et al., 2008]. Additionally, mitochondria regulate calcium homeostasis [Chen et al., 2005; O' Rourke, 2004; Vandecasteele et al., 2001] and produce reactive oxygen species (ROS) [Chen et al., 2003; Miyamoto et al., 2005]. Thus, mitochondria play a critical role in the cells.

However, the dysfunction of mitochondria is related to a variety of pathological processes and diseases. For example, changes in mitochondrial function and ultrastructure have been observed in mental disorders [Gong et al., 2011]. Mitochondrial DNA (mtDNA) mutations and deletions [Kujoth et al., 2005], and ROS over production [Lemieux et al., 2010] have been shown to contribute to the aging process. The decreased expression of mitochondrial genes [Hsieh et al., 2004] and disrupted mitochondrial structure have been associated with abnormal human development [Au et al., 2005]. Mitochondria form dynamic networks, and constantly undergo fission and fusion to maintain their integrity and quantity [Detmer and Chan, 2007]. The impaired balance of mitochondrial fission and fusion [Wang et al., 2009] and altered morphology of the cristae [Baloyannis, 2006] are related to Alzheimer's disease. Furthermore, a deficiency in electron transport chain has been noted in diabetes [Ritov et al., 2010].

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Given the important role of mitochondria in controlling the cellular physiology and the potential of deregulated mitochondria to cause pathology, it is necessary to understand the molecular regulation of mitochondrial metabolism, structure and function.

MicroRNAs (miRNAs)

miRNAs are a class of small noncoding RNAs about 22 nucleotides long, and they can bind to the 3′ un-translated region (3′UTR) of mRNAs, thereby inhibiting mRNA translation or promoting mRNA degradation [Lee et al., 2003]. This miRNA mediated regulation is sequence-specific and occurs at post-transcriptional level [He and Hannon, 2004]. Recently, miRNA has been also shown to target 5′ UTR or the open reading frames of targeted mRNA [Moretti et al., 2010]. miRNAs have been found in mitochondria [Bian et al., 2010; Kren et al., 2009], and they can contribute to mitochondrial dysfunction [Li et al., 2011]. Growing evidence has demonstrated that miRNA can play a significant role in the regulation of development, differentiation, proliferation, apoptosis as well as tumorigenesis [Cai et al., 2009]. Therefore, there is considerable interest in exploring regulation of mitochondria by miRNAs. This review is focused on recent findings concerning the role of miRNAs in controlling mitochondrial function.

miRNAs can affect mitochondrial metabolism

A fundamental function of mitochondria is to produce ATP through oxidative phosphorylation, thereby providing energy for the cellular activities. Mitochondria have their own genome, transcription and translation systems, but they also require proteins encoded by the nucleus [Cannino et al., 2007]. Cytochrome c oxidase IV (COXIV) is a key nuclear-encoded protein within the electron transfer chain in mitochondria, and participates in ATP production. The alteration of COXIV protein levels is able to affect mitochondrial function. miR-338 is a brain-specific miRNA expressed in neuronal tissue [Kim et al., 2004; Wienholds et al., 2005]. The miR-338 has been shown to regulate the expression of COXIV. COXIV 3′UTR contains miR-338 target And enforced expression of miR-338 reduces COXIV mRNA as well as protein levels. On the contrary, inhibition of endogenous miR-338 by its specific antagomir results in an increase in COXIV mRNA and protein levels. Functional study revealed that the over expression of miR-338 can significantly reduce mitochondrial oxygen consumption, mitochondrial metabolic activity, and ATP production [Aschrafi et al., 2008].

Glutaminase is important for mitochondrial metabolism and it converts glutamine to glutamate, which is further catabolized through the tricarboxylic acid cycle for the production of ATP or serves as the substrate for glutathione synthesis in mitochondria. The miR-23a and miR-23b (miR-23a/b) have been demonstrated to participate in targeting glutaminase [Gao et al., 2009] and can directly repress glutaminase expression. Modulation of miR-23a/b through their antagomirs can affect glutaminase expression levels.

The miR-210, a miRNA significantly upregulated during hypoxic stress in many cell types [Corn, 2008; Kulshreshtha et al., 2007], is reported to be involved in repressing mitochondrial respiration and the associated downstream functions [Chan et al., 2009; Favaro et al., 2010]. For example, mitochondrial iron sulfur cluster homologue (ISCU) has been identified as a target of miR-210. Iron sulfur clusters are assembled in mitochondria by a complex series of chaperones and enzymes [Mühlenhoff and Lill, 2000], which are then exported to the cytoplasm for assembling into the relevant functional protein [Rouault and Tong, 2008; Tong and Rouault, 2000]. A decrease in ISCU can influence the activity of enzymes requiring iron sulfur clusters. The miR-210 can repress the expression of ISCU by directly binding to ISCU 3′UTR. Both gain-and loss-of-function assays have demonstrated that miR-210 is necessary and sufficient for the downregulation of ISCU during hypoxia.

Consequently, miR-210 is able to affect aconitase and the activity of mitochondrial complex.

Certain miRNAs are able to regulate insulin gene expression, biosynthesis and the secretion [Herrera et al., 2010; Poy et al., 2004; Xia et al., 2011; Zampetaki et al., 2010]. For example, miR-15a promotes insulin biosynthesis by inhibiting the expression of endogenous uncoupling-protein 2 (UCP-2) in mouse β-cells. The UCP-2 is a member of the mitochondrial inner membrane carrier family of proteins and it facilitates uncoupling of oxygen consumption [Bordone et al., 2006; Bouillaud et al., 1985]. The miR-15a regulates oxygen consumption and ATP generation through targeting UCP-2. Mitochondrial dysfunction is related to insulin resistance [Cheng et al., 2009; Kim et al., 2008; Lowell and Shulman, 2005], but the underlying mechanism is not fully understood. A recent report shows that miR-126 is actively involved in insulin resistance by targeting insulin receptor substrate-1 (IRS-1) [Ryu et al., 2011]. Thus, miRNAs can be considered as a target for developing effective treatment for diabetes.

Interestingly, miR-696 regulates fatty acid oxidation capacity and mitochondrial biogenesis through targeting peroxisome proliferator-activated receptor gamma co activator 1-alpha (PGC-1α) [Aoi et al., 2010]. The PGC-1α promotes aerobic metabolism and mitochondrial biogenesis in skeletal muscle [Puigserver et al., 1998; Wu et al., 2002; Wu et al., 1999]. Both the fatty acid oxidation and mtDNA content are reduced by miR-696 over expression but increased upon transfection of its inhibitor.

miRNAs participate in the regulation of mitochondria-mediated apoptosis

Apoptosis can be initiated though the extrinsic and/or intrinsic pathways. The extrinsic pathway is initiated by the binding of death ligands such as Fas ligand (FasL) or tumor necrosis factor α (TNF-α) to their corresponding death receptors, Fas or TNF receptor-1 (TNFR-1), respectively. Upon ligand binding, the death receptors undergo trimerization and recruit Fas-associated death domain protein (FADD) that then associates with procaspase-8 to form death-inducing signaling complex (DISC) [Li et al., 2010b]. However, the intrinsic pathway is initiated through mitochondria. A death signal induces the release of mitochondrial pro-apoptotic proteins such as cytochrome c [Li et al., 1997], mitochondrial apoptosis-inducing factor [Susin et al., 1999] and Smac/Diablo [Du et al., 2000; Verhagen et al., 2000]. Cytochrome c forms a complex with Apaf-1 and procaspase-9 resulting in the activation of caspase-9. Smac/Diablo can associate with inhibitor of apoptosis proteins thereby counteracting their inhibitory effects on caspases. The intrinsic pathway is regulated by the Bcl-2 family members. For example, in response to proapoptotic stimuli, the cytosolic Bax and Bad translocate to mitochondria and permeabilize the outer mitochondrial membrane leading to the release of proteins in the mitochondrial intermembrane space into the cytosol. In contrast, Bcl-2 and Bcl-xL are able to associate with Bax and Bad thereby quenching their death inducing potential [Antignani and Youle, 2006; Cleland et al., 2011; Karbowski et al., 2006].

The miR-15a and the miR-16-1 (miR-15a/16-1) induce apoptosis through the regulation of mitochondrial function. They reside as a cluster at the chromosomal region 13q14 and are frequently deleted or down-regulated in chronic lymphocytic leukemia [Calin et al., 2005]. miR-15a and 16-1 regulate multiple oncogenic activities including Bcl-2 and Mcl1. Further, miR-15a promotes mitochondrial dysfunction indicated by cytochrome c release into the cytosol and the disruption of mitochondrial membrane potential [Gao et al., 2010]. The miR-143 is specifically expressed in normal colon cells, and its expression is decreased in human colon cancer tumors. ERK5 stimulates cell proliferation [Nishimoto and Nishida, 2006] and it has been identified as a target of miR-143 [Akao et al., 2006]. Induction of

apoptosis by interfering with mitochondrial function can be mediated through miR-143 targeting of ERK5 pathway [Nakagawa et al., 2007]. The miR-1 is a muscle specific miRNA [Chen et al., 2006]. Upon apoptotic stimulation, the miR-1 expression is increased with a concomitant release of cytochrome c from mitochondria and a decrease in membrane potential [Yu et al., 2008].

miRNAs control mitochondrial morphology

Mitochondria constantly undergo biogenesis, fusion and fission. They form dynamic networks that are necessary for the maintenance of organelle fidelity [Berman et al., 2008; Cassidy-Stone et al., 2008; Edwards et al., 2010; Tatsuta and Langer, 2008; Yang et al., 2008]. The morphological integrity of mitochondria is vital for their function. Mitochondrial biogenesis involves mitochondrial DNA replication and mass increase. In contrast, mitochondrial DNA replication does not occur during mitochondrial fission. Instead, the existing mitochondrial DNA divides into the newly fission mitochondria [Berman et al., 2008; Tatsuta and Langer, 2008]. Upon fission mitochondrial numbers are increased while their sizes are decreased. The mitochondrial fusion and fission participate in the regulation of apoptosis. Mitochondrial fusion is able to inhibit apoptosis, whereas mitochondrial fission is involved in the initiation of apoptosis [Cassidy-Stone et al., 2008]. Excessive mitochondrial fission is involved in the pathogenesis of many diseases such as diabetic neuropathy [Edwards et al., 2010] and brain and skeletal muscle disorders [Yang et al., 2006; Yang et al., 2008].

miRNAs have been recently shown to be involved in controlling mitochondrial dynamics. The miR-30 family includes 5 members, miR-30a, miR-30b, miR-30c, miR-30d and miR-30e, and they are abundantly expressed in the heart. miR-30a, miR-30b and miR-30d levels were decreased substantially upon hydrogen peroxide treatment, whereas miR-30c and miR-30e levels remained unaltered. In searching for the downstream targets, p53 was identified as the direct target of miR-30 family members. Mitochondrial fission requires the activity of a dynamin-related protein-1 (DRP1) [Frank et al., 2001], which is a GTPase that causes scission of the mitochondrial outer membrane, resulting in fission of mitochondrial tubules into fragments. The p53 activates Drp1 transcriptionally and consequently leads to apoptosis. Thus the miR-30 family members can regulate mitochondria fission and apoptosis through p53 and Drp-1 axis [Li et al., 2010a].

The miR-499 encoded by intron of myosin gene is a cardiac-abundant miRNA under physiological conditions [Kim et al., 2006; van Rooij et al., 2009], but is down-regulated during apoptosis. The miR-499 can prevent apoptosis by targeting calcinurin, which dephosphorylates and activates Drp1, resulting in fission of mitochondria and apoptosis. Interestingly, the expression of miR-499 is also transcriptionally regulated by p53 [Wang et al., 2011].

Despite the fact that several miRNAs are involved in the mitochondrial fission machinery, the maintenance of mitochondrial equilibrium is very complex. Other factors such as mitofusion and Fis-1 are vital in regulating mitochondrial fusion and fission. The detailed molecular mechanism of miRNAs in regulating the mitochondrial network remains largely unknown.

miRNAs are present in mitochondria

miRNAs are known to be encoded by nuclear genome and to modulate gene expression mainly in the cytosol. Intriguingly, recent studies using a miRNA microarray system to survey miRNA expression at a genome-wide scale in the rigorously purified mitochondria found that unique miRNAs are enriched in mitochondria independent of total cellular

abundance [Bandiera et al., 2011; Barrey et al., 2011; Bian et al., 2010; Kren et al., 2009]. However, miRNAs retained in mitochondria are cell type-dependent. 15 nuclear encoded miRNAs are uniquely and reproducibly identified in mitochondria isolated from adult rat livers [Kren et al., 2009]. Twenty miRNAs are reported in mouse liver mitochondria including miR-122, miR-805 and miR-609 [Bian et al., 2010]. In the mitochondria isolated from the human myotubes there are more than twenty miRNAs [Barrey et al., 2011]. Thirteen miRNAs such as miR-1973, miR-1275 and miR-494 are significantly enriched in the mitochondria from HeLa cells [Bandiera et al., 2011]. These findings, and the miRNAs present in mitochondria are summarized in Table 1.

Not only miRNAs are present in mitochondria, other components of miRNA machinery are also detectable in mitochondria. For example, miRNAs require binding to the RNA-induced silencing complex (RISC) before they can modulate the expression of their target genes [Parker and Sheth, 2007]. The argonaute Ago2 is the main and a key active protein of the RISC complex. Recently, it is shown that Ago2 is present in mitochondria [Bandiera et al., 2011; Bian et al., 2010].

The physiology and pathology of miRNAs in mitochondria remain unknown. Streptozotocin (STZ) is known to induce type 1 diabetes and mitochondrial dysfunction [Ghosh et al., 2004]. Mitochondria-associated miRNAs are significantly altered upon STZ treatment, with miR-494, miR-202-5p, miR-134 and miR-155 increased, while miR-705 and miR-122 decreased [Bian et al., 2010]. Elucidating the roles of miRNAs in mitochondria will provide the basic framework to investigate their functions in mitochondria and to unravel their potential in designing new therapeutic strategies for mitochondrial diseases.

miRNA and mitophagy

Autophagy is a process of catabolism of cellular components, and necessary for the maintenance of cell homeostasis [Mortensen et al., 2010; Yang and Klionsky, 2010]. It is induced by nutrient deprivation and a variety of physiological and pathological conditions. The morphological character of autophagy is autophagosome formation that encompasses the cellular components, and fuses with lysosome to degrade it. Mitophagy is a type of autophagy, which selectively degrades mitochondria [Kim et al., 2007]. Mitophagy regulates mitochondria number to match metabolic or developmental demand [Kundu et al., 2008], and also is a form of quality control to remove damaged mitochondria [Kundu et al., 2008; Okamoto K, 2009; Tolkovsky et al., 2002]. In mammalian cells, upon mitochondrial membrane depolarization PINK1 triggers Parkin translocation from cytosol to mitochondria where Parkin ubiquitylates mitochondrial proteins [Geisler et al., 2010], thereby inducing damaged mitochondria to form autophagosomes (Figure 1).

Recent work has suggested a role for miRNAs in autophagy, including miR-101 [Frankel et al., 2011], miR-204 [Xiao et al., 2011], miR-30a [Zhu et al., 2009]. miRNAs target transcripts of autophagy-related proteins thereby influencing their function in autophagy. For example, Parkin functions in a pathway that links ubiquitylation with mitophagy [Geisler et al., 2010]. In Parkinson’s disease miR-34b/c downregulation is an early event [Miñones-Moyano et al., 2011]. It remains to be elucidated as to whether the early deregulation of miR-34b/c is responsible for the downstream transcriptome alterations underlying mitochondrial dysfunction. In some human tumors, miR-21 levels are significantly increased, and it down regulates the expression of PTEN [Meng et al., 2007; Zhang et al., 2010]. The PTEN regulates PINK1 that is involved in mitophagy pathway (Fig. 1). Further investigations are required to clearly elucidate the exact mechanism by which miRNAs control autophagy and mitophagy.

Perspective

It is obvious that miRNAs play a critical role in regulating mitochondrial function under physiological and pathological conditions. The relationship between the aberrant distribution of miRNAs in mitochondria and mitochondrial dysfunction needs to be fully established. Mitochondrial dysfunction is related to a variety of diseases. miRNAs have been used as diagnostic biomarkers in some of the diseases [Cogswell et al., 2008]. However, specific miRNAs that can be employed as diagnostic markers for mitochondria-related diseases have to be identified and validated. Further understanding of the specific functional consequence of modulating miRNA levels may eventually lead to miRNAs-based therapy for the treatment of mitochondria-related diseases. Overall, the elucidation of miRNAs in regulating mitochondrial activities may fill some of the gap in the knowledge on the aspects of cell biology and the pathogenesis of diseases, and may eventually lead to the development of pharmacological interventions for mitochondrial diseases.

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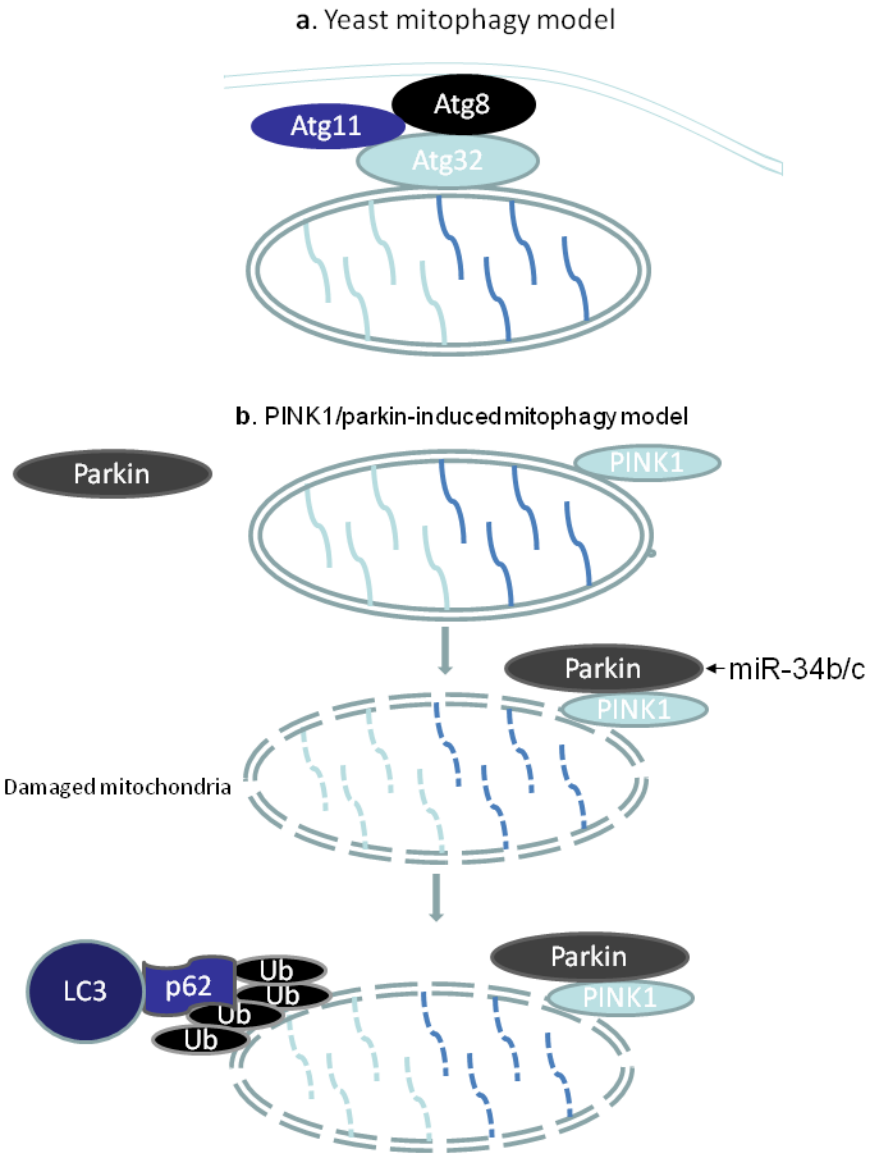

Figure 1. A schematic model of mitophagy

a. In yeast, Atg32 interacts with Atg 8 and Atg11 to recruit mitochondria into autophagosomes. **b**. PINK1/parkin-induced mitophagy in mammals. In the absence of mitochondrial injury, Parkin is located in cytosol. Upon mitochondrial damage, PINK1 triggers Parkin translocation to mitochondria where Parkin ubiquitylates mitochondrial proteins. This leads to the association of p62 with LC3, resulting in autophagosome formation.

Table 1

miRNAs identified in mitochondria from different tissue or cell types

Adult rat liver	Mouse liver	Human myotubes	HeLa cell line
miR-130a	miR-122	miR-720	miR-1973
miR-130b	miR-805	miR-133b	miR-1275
miR-140*	miR-690	miR-1974	miR-494
miR-320	miR-689	miR-24	miR-513a-5p
miR-494	miR-494	miR-133a	miR-1246
miR-671	miR-705	miR-125a-5p	miR-328-5p
miR-202	miR-721	miR-1979	miR-1908
miR-705	miR-720	miR-103	miR-1972
miR-709	miR-188-5p	miR-125b	miR-1977
miR-721	miR-101	miR-103	miR-638
miR-761	let-7f	miR-221	miR-1974
miR-763	miR-711	miR-23a	miR-1978
miR-198	miR-432	let-7b	miR-1201
miR-765	miR-181b	miR-423-3p	
	miR-361-5p	miR-106a	
	miR-680	miR-23b	
	miR-181d	miR-92a	
	miR-29c	miR-193b	
	miR-29a	miR-365	
	miR-762	miR-93	