DNA AND CELL BIOLOGY
Volume 39, Number 8, 2020

Pp. 1379–1384
DOI: 10.1089/dna.2019.5013

Biological and Clinical Relevance of microRNAs in Mitochondrial Diseases/Dysfunctions

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Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and a denosine triphosphate synthesis machinery. Occurrences of mitochondrial dysfunction are due to genetic or environmental changes in the mitochondria or in the nuclear DNA that codes mitochondrial components. Currently, drug options are available, yet no treatment exists in sight of this disease and needs a new insight into molecular and signaling pathways for this disease. microRNAs (miRNAs) are small, endogenous, and noncoding RNAs function as a master regulator of gene expression. The evolution of miRNAs in the past two decades emerged as a key regulator of gene expression that controls physiological pathological cellular differentiation processes, and metabolic homeostasis such as development and cancer. It has been known that miRNAs are a potential biomarker in both communicable and noncommunicable diseases. But, in the case of mitochondrial dysfunction in miRNAs, the number of studies and investigations are comparatively less than those on other diseases and dysfunctions. In this review, we have elaborated the roles of miRNAs in the mitochondrial diseases and dysfunctions.

Keywords: pre-miRNA, microRNA, mitochondrial dysfunction, mitochondrial disease, biomarker, diagnostic

Introduction

To sustain life and to support organ functions, our body requires >90% of energy, which is possible through mitochondria ''the power house of the cell.'' Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP synthesis machinery (Nicolson, 2014). Mitochondrial dysfunction has been correlated with metabolic diseases such as obesity, diabetes mellitus type 1 and type 2 (Cheng and Almeida, 2014), age-related diseases, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease (Arun *et al.*, 2016; Grimm *et al.*, 2016), cancer (Sotgia *et al.*, 2011; Jezierska-Drutel *et al.*, 2013), and majorly cardiovascular diseases (Limongelli *et al.*, 2012).

microRNAs (miRNAs) are single-stranded small noncoding RNAs mainly transcribed as long primary transcripts in the nucleus and subsequently cleaved to form stem loop structured precursor molecules of 70 nt in length (pre-miRNAs) by Drosha (Panagal *et al.*, 2018). The precursor stem loop structure is then transported to the cytoplasm, later they are acted upon by an enzyme RNase III Dicer to produce 22 nt mature miRNAs (Panagal *et al.*, 2018). In general, mature miRNAs can identify their cognate messenger RNA (mRNA) and bind its 3′ end of the untranslated region (UTR) for the post-transcriptional repression activity (Panagal *et al.*, 2018, 2019).

There are a number of miRNAs that have been distinguished and characterized in human diseases (Wang *et al.*, 2019). miRNAs, which translocate into the mitochondria, are known as mitochondrial miRNA (mitomiR). It has been established that mitomiRs can regulate gene expression, suggesting that after translocation, mitomiRs can bind to the 3′-end of a mitochondrial gene, altering its regulation. miRNAs perform as antiregulators of gene expression

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(Giuliani *et al.*, 2017). Interestingly, there are so many miRNAs that play an important role in the mitochondrial diseases and dysfunctions, for example, miR-122, miR-762, and miR-217 (Tang *et al.*, 2019; Wang *et al.*, 2019; Yan *et al.*, 2019).

The evolution of miRNAs in the past two decades emerged as a key regulator of gene expression that controls physiological pathological cellular differentiation processes and metabolic homeostasis (Sekar *et al.*, 2016a, 2016b; Sekar *et al.*, 2019a, 2019b). miRNAs are a potential biomarker in both communicable and noncommunicable diseases. But, in the case of mitochondrial dysfunction in miRNAs, the number of studies and investigations are comparatively less than those of other diseases and dysfunctions. In this review, we have elaborated on the roles of miRNA in mitochondrial diseases and dysfunctions.

Relationship of miRNAs in mitochondrial diseases and dysfunctions

It has been suggested that miRNAs are involved in many biological processes, including proliferation, migration, invasion differentiation, and apoptosis (Giuliani *et al.*, 2017; Panagal *et al.*, 2018, 2019). Despite miRNAs being involved in several diseases and their role been clearly delineated (Sekar *et al.*, 2019a, 2019b), up to our knowledge, publications related to miRNAs in mitochondria and its related diseases are very less; we summarize hereunder some of the research evidence from those published articles.

Recently Giuliani *et al*. (2017) illustrated the role of miRNAs on mitochondria in senescence. In that article, they explained that miR-146 was translocated into mitochondria and alters the energetic, oxidative, and inflammatory status of senescent cells, suggesting that miRNA-146 is involved in aging-induced inflammation, thereby reducing the aging rate and postponing the development of age-related disorders (Giuliani *et al.*, 2017).

It has been reported that the mitochondrial deacetylase sirtuin 3 (SIRT 3) plays a major role in the maintenance of mitochondrial function by regulating the mitochondrial acetylome in myocardial issues. In contrast, several miRNAs have been associated with cardiac remodeling by modulating key signaling elements in the myocardium. In particular, miR-195 has been identified as a molecule that downregulates the SIRT 3 expression by directly targeting its 3′ UTR and altering the cardiac energy metabolism through elevated PDH acetylation levels and raised ATP synthase (Zhang *et al.*, 2018).

A study by Koh *et al*. (2016) has reported that mitochondrial activity in human white adipocytes is regulated by the ubiquitin carrier protein 9/miRNA-30a axis. UBC-9 and miRNA-30a exhibit an inverse expression in adipose tissue, and miRNA-30a is robustly elevated in brown fat only. Depletion of UBC-9 by SiRNA of miRNA-30a mimics in human white adipocytes reflected features of brown fat cells. Their results showed that UBC-9 depletion induced a brown fat gene program in human subcutaneous adipocytes, suggesting that browning effect protects against obesity-induced metabolic diseases in humans and animal models of type 2 diabetes mellitus (T2DM; Koh *et al.*, 2016).

Wu *et al.* (2017) reported that the expression of miRNA-1224-5p mediates mitochondria damage in lung tissues of silica-induced pulmonary fibrosis and fibroblasts exposed to TGF-β1. Suppression of miR-1224-5p hampers the progression of silica-induced fibrosis *in vivo* and TGF-β1-induced myofibroblast differentiation *in vitro* (Wu *et al.*, 2017).

Rippo *et al.* (2014) worked on endothelial cells, a well-established model of replicative senescence, where the results revealed that miRNA-146a, miRNA-34a, and miRNA-181a are upregulated and conversely their target Bcl-2 is downregulated. Interestingly, Bcl-2 an antioxidant antiapoptotic factor that regulates mitochondrial fission/fusion and autophagy critically involved in maintaining mitochondrial integrity plays an important role by controlling the mitochondrial function and dysfunction during cellular aging. Their report concluded that aging-related mitochondrial miRNAs may play a regulatory role by regulating mitochondrial protein expression (Rippo *et al.*, 2014). Figure 1 shows the role of miRNA in mitochondrial function/dysfunction.

Another miRNA, miR-145, has been attributed to regulating mitochondrial apoptotic pathway in the heart challenged with oxidative stress. It is hypothesized that miR-145

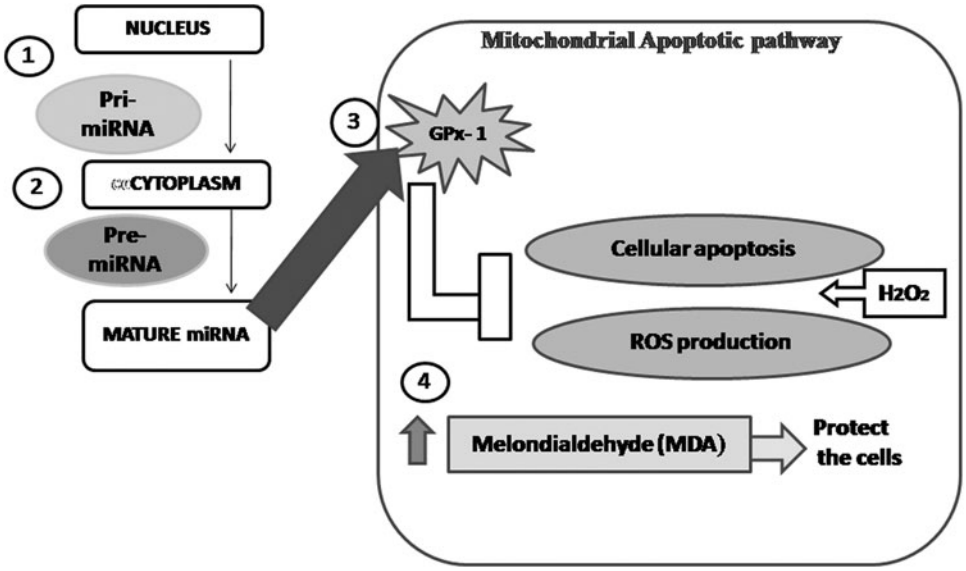

FIG. 1. The process of miRNA (1) from the nucleus pre-miRNA transport to the cytoplasm, (2) in the cytoplasm pre-miRNA converts to mature miRNA, (3) the mature miRNA regulates the mitochondrial apoptotic pathway, (4) mature miRNA suppresses or induces the disease progression. miRNA, microRNA.

may represent a potential therapeutic target for treating oxidative stress associated with cardiovascular disease such as myocardial ischemia/reperfusion injury (Li *et al.*, 2012).

A recent report stated that noncoding RNAs such as miRNA act as a responsible gene regulator and has been involved in cellular signaling pathways. Yan *et al*. (2019) reported on miR-762, a new miRNA in the mitochondrial dysfunction. miR-762 is predominantly translocated in the mitochondria and was significantly upregulated upon anoxia/reoxygenation (A/R) treatment. Knockdown of endogenous miR-762 considerably attenuated the decrease in intracellular ATP levels, increase in reactive oxygen species (ROS) levels, the decrease in mitochondrial complex I enzyme activity, and the increase in apoptotic cell death in cardiomyocetes, which was induced by A/R treatment. Enforced expression of miR–762 dramatically decreased the protein levels of endogenous NADH dehydrogenase subunit 2 (ND2) but had no effect on the transcript level of ND2. Inhibitory effect of miR-762 downregulation was attenuated by ND2 knockdown, concluding that miR-762 may yield a fresh therapeutic target for myocardial infarction (Yan *et al.*, 2019).

Dahlmans *et al*. (2017) have mentioned about decreased mitochondrial function playing an important role in numerous pathologies, including cardiomyopathy, cancer, neuromuscular degeneration, Alzheimer's disease, and T2DM. A diminished mitochondrial oxidative capacity in skeletal muscle tissue has frequently been reported in humans with T2DM and insulin resistance. They also revealed that miR-199a and miR-214 have been upregulated during myocardial hypoxia and elevated in cardiac biopsies of heart failure patients and actively repress the peroxisome proliferator-activated receptor (PPARδ), a well-known transcription factor in the regulation of mitochondrial metabolism. Interestingly from a therapeutic standpoint, *in vivo* silencing of miRNAs with specific antagomirs resulted in a restoration of PPARδ levels, normalization of mitochondrial fatty acid oxidation, and rescue of cardiac failure. In addition, they quantified the expression of miRNAs in skeletal muscle biopsies of endurance—trained athletes, lean and obese, sedentary subjects, and type 2 diabetic patients, and found that the expression of validated miRNAs showed a strong relationship with *in vivo* mitochondrial function in humans (Dahlmans *et al.*, 2017).

A research article by Galvan *et al*. (2017) on miR-93 which is a hallmark miRNA in diabetic status has been shown to be downregulated. In addition, they also illustrated on miR-21, a well-known miRNA known to be upregulated in patients with a variety of kidney diseases and in animal models of chronic kidney disease. They concluded that mice lacking miR-21 were guarded against kidney fibrosis, enhancing through mitochondrial fatty acid oxidation and targeting of α PPAR (Galvan *et al.*, 2017).

Interestingly, a study by Wen *et al*. (2018) on resistin levels that is associated with steatohepatitis and nonalcoholic fatty liver disease confirmed that miR-34a has been upregulated by resistin and mediated by CCAAT/enhancer-binding protein beta (C/EBPβ). Furthermore, miR-34a inhibits the PPAR α signaling pathway by binding to sites in the 3′ UTR of adipoR2 genes and also involved in the 5′-adenosine monophosphate-activated protein kinase pathway in mitochondria (Wen *et al.*, 2018).

Li *et al*. (2016) in their study showed a remarkable upregulation of miR-144-3p with increased expression of key genes involved in maintaining the mitochondrial function, including peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), nuclear respiratory factor 1, and mitochondrial transcription factor A. In the same cells, miR-144-3p overexpression significantly inhibited the protein expression of β-amyloid precursor protein (APP). In the same study, noticeable increase in cellular ATP, cell viability, and the relative copy number of mitochondrial DNA was noted, suggesting that miR-144-3p plays an important role in maintaining mitochondrial function, along with its target gene APP (Li *et al.*, 2016).

Interestingly, Liu *et al.* (2018) reported that miR-138 mimic promoted the proliferation and mitochondrial membrane potential levels in human pulmonary artery smooth muscle cells (HPASMCs), suggesting that miR-138 promotes proliferation and suppresses mitochondrial depolarization of HPASMCs by targeting TASK-1gene.

Wang *et al*. (2014) identified a miRNA that targets glutathione peroxidase-1 an important intracellular antioxidant enzyme that enzymatically quenches hydrogen peroxide to water and limits its harmful effects (GPx 1) and maintains redox homeostasis. They used quantitative real-time PCR that demonstrated the markedly upregulated expression of miR-181a in H_2O_2-treated H_9C_2 cells and the down regulation of miR-181a correlated with inhibition of H_2O_2-induced cellular apoptosis, ROS production, and increase in melondialdehyde (OA) levels. Their results suggested that miR-181a plays an important role in regulating the mitochondrial apoptotic pathway in cardiomyocytes provoked by oxidative stress. It is also considered as a potential therapeutic target for the treatment of oxidative stress-associated cardiovascular diseases (Wang *et al.*, 2014). Figure 2 shows the miRNA regulation on mitochondrial apoptotic pathway.

An interesting study by Jeong *et al*. (2013) elaborated on mitochondrial dysfunction by impairment of insulin signaling in SK-Hep 1 cells through a reduction in the expression of IRS-1 3′ UTR. Using a reporter gene assay they confirmed that miR-96 authentically targeted IRS-1 gene 3′ UTR, and also the ectopic expression of miR-96 caused a substantial decrease in ITR-1 protein expression and a consequent impairment in insulin signaling. They suggested that upregulation of miR-96 by mitochondrial dysfunction contributes to the development of insulin resistance by targeting IRS-1 in SK-Hep 1 cells (Jeong *et al.*, 2013).

The research article by Jiang *et al*. (2013) found that mitochondrial uncoupling protein 2 (UCP2) was induced in kidney tubular epithelial cells. In NRK-52E cells, TGF-β1 remarkably induced UCP-2 expression and the knockdown of UCP 2 mRNA largely abolished the effect of TGF-β1. Moreover, they found that the UCP 2 mRNA is a direct target of miR-30e. Conversely, miR-30e mimics significantly inhibit TGF-β1, whereas miR-30e inhibitor imitates TGF-β1 effect on the NRK-52E cells. Thus, they conclude that the mitochondrial miR-30/UCP2 axis has an important role in mediating TGF-β1-induced epithelial–mesenchymal transition and kidney fibrosis. Targeting this pathway may shed new light for the future of fibrotic kidney disease therapy (Jiang *et al.*, 2013).

Thus from the discussed studies, one can see the correlation between several miRNAs and mitochondria in various

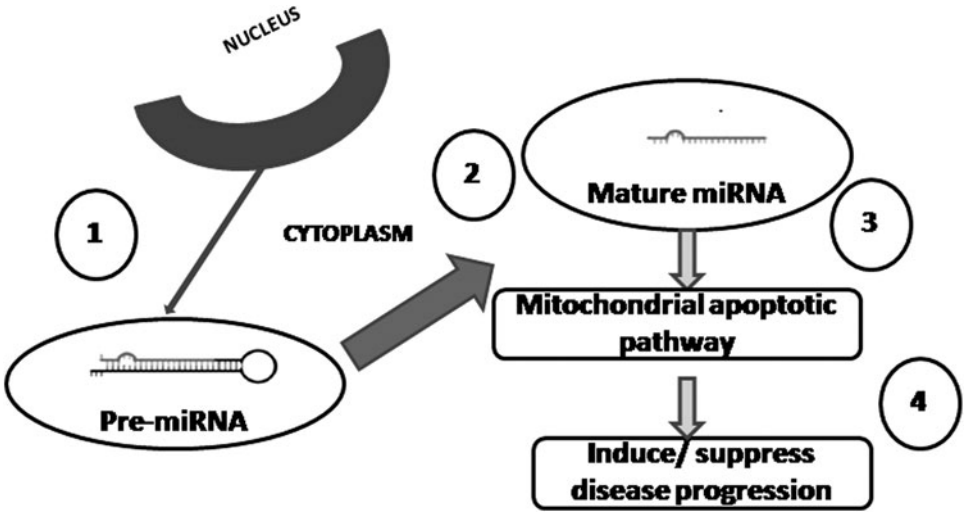

FIG. 2. (1) The primary miRNA from the nucleus reaches the cytoplasm; (2) in the cytoplasm, the pre-miRNA processed to form a mature miRNA; (3) miRNA targets the glutathione peroxidase; (4) downregulated miRNA blocks H_2O_2-induced cellular apoptosis, reactive oxygen species production, and increases melondialdehyde levels regulating the apoptotic pathway in an oxidative stress-associated cardiovascular disease.

diseases and disorders. Moreover, the miRNA seems to have a pivotal role in initiation and progression of various pathologies mediated by affecting mitochondrial functions. Some miRNAs upregulation seems to exert a beneficial role through mitochondrial intervention in reversing the pathogenesis and protection against various metabolic conditions. From a therapeutic viewpoint, these miRNAs and their mimics show a promising future and opens new avenues in diseases management and prognosis through mitochondrial energy-dependent pathways. However, there is a huge lacuna on deciphering the exact role of those miRNAs on mitochondria-mediated pathogenesis and alleviatory effects. Hence there is a need for future functional studies in this emerging discipline.

Clinical Perspective and Future Directions

miRNAs are believed to be the most important dictatorial molecules in the cells and controlling broad variety of cellular functions such as proliferation, migration, invasion, and apoptosis (Sekar *et al.*, 2016a, 2016b; Bai *et al.*, 2019). miRNAs interact with the mRNAs at the post-transcriptional levels and regulate the gene expression by either repression or degradation of the translation mechanisms. In general, miRNAs are considered a key regulator for breast cancer progressions and are readily detected in all kinds of body fluids including serum, blood, urine, and semen (Humphries *et al.*, 2019; Li *et al.*, 2019). In this perspective, understanding the role of miRNAs in mitochondria is significant and it may open the gateway for the discovery or the identification of new prognostic, diagnostic, or therapeutic targets for mitochondrial dysfunction or its related diseases. Interestingly, many articles show that the potential impact of miRNAs as a biomarker for mitochondrial dysfunction and their interaction with surrounding molecular pathways (Jeong *et al.*, 2013; Jiang *et al.*, 2013; Wang *et al.*, 2014; Li *et al.*, 2016; Liu *et al.*, 2018).

miRNAs that are present in the mitochondrial fraction and alter the mitochondrial function are called mitomiR (Srinivasan and Das, 2015). Among the reported miRNAs, miR-1291, miR-138, miR-150, miR-199a-3p, and miR-532-5p are involved in modifying the expression of key glycolytic

Table 1. Differentially Expressed microRNAs Involved in Mitochondrial Pathways

Type of disease	*Status of miRNAs expression*	*miRNAs*	*References*
Mitochondrial dysfunction	Upregulated in (A/R) treatment downregulated in ND2 knockdown	miRNA-762	Yan *et al.* (2019)
Heart failure patients	Upregulated in (PPAR δ)	miRNA-199a miRNA-124a	Dahlmans *et al.* (2017)
Diabetes mellitus	Downregulated	miRNA-93	Galvan *et al.* (2017)
Kidney chronic disease (In mice model)	Upregulated	miRNA-21	Galvan *et al.* (2017)
Liver disease	Upregulated in (PPAR α)	miRNA-34a	Wen *et al.* (2018)
Mitochondrial function	Downregulated in (MPTP) Upregulated in (PGC-1α), (NRF-1), (TFAM)	miRNA-144-3p	Li *et al.* (2016)
Parkinson's disease	Downregulated in (NF-κB)	miRNA-7	Choi *et al.* (2014)
Tumor suppression	Upregulated in (MM)	miRNA-216	Tomasetti *et al.* (2014a,b)
Mitochondrial dysfunction	Upregulated in (IRS-1)	miRNA-96	Jeong *et al.* (2013)
Kidney fibrotic disease	Downregulated in (TGF-β1)	miRNA-30e	Jiang *et al.* (2013)

A/R, anoxia/reoxygenation; miRNAs, microRNAs; MM, malignant mesothelioma; NF-κB, nuclear factor-κB; NRF-1, nuclear respiratory factor 1; PPAR, peroxisome proliferator activated receptor; TFAM, mitochondrial transcription factor A.

enzymes, including glucose transporters, suggesting that mitochondrial glucose uptake can be modified by mitomiR (Srinivasan and Das, 2015). The mitochondrial fission and fusion machinery is very important to eliminate unwanted mitochondrial fraction from the cells (Wang *et al*., 2011). Interestingly, mitochondrial fission 1 protein (Fis1) is targeted by miR-484, since Fis1 is considered as a necessary protein for mitochondrial fission and apoptosis (Wang *et al*., 2011). So mitomiR plays an important role in the mitochondrial dysfunctions by targeting various proteins and signaling pathways that are essential for regular mitochondrial function.

A review of Tomasetti *et al.* (2014a,b) illustrated that the modulation of miRNA levels may provide a new therapeutic approach for the treatment of mitochondrial-related pathologies, including neoplastic diseases. Interestingly, Kato *et al.* (2013) described the role of miRNAs in the pathobiology of various diabetic complications and their involvement in oxidative stress. They revealed the potential use of differentially expressing miRNAs as novel diagnostic biomarkers and therapeutic targets, suggesting that miRNAs act as a potential mediator and biomarker of diabetic complications (Kato *et al.*, 2013).

Recent research suggested that miRNAs are potential biomarkers in both communicable and noncommunicable diseases (Sekar *et al.*, 2016a, 2016b; Bai *et al.*, 2019; Humphries *et al.*, 2019; Li *et al.*, 2019). In contrast, in the case of mitochondrial dysfunction in miRNAs, the number of studies and investigations are comparatively less than those of other diseases and dysfunctions. We still require more research to prove that miRNAs are a vibrant prognostic, diagnostic, and therapeutic biomarker for mitochondrial dysfunction. Surprisingly, Tomasetti *et al.* (2014a,b) summarize the role of miR-126 in the malignant mesothelioma (MM) H28 cell lines affects the mitochondrial energy metabolism, reduces mitochondrial respiration, and promotes glycolysis. Furthermore, the mentioned parameters resulted in suppression of MM, and miR-126 may act as a therapeutic option for fatal neoplastic disease (Humphries *et al.*, 2019). Another study by Choi *et al.* 2014 also summarized on downregulation of relA, a component of nuclear factor-κB (NF-κB) associated with miR-7. Their findings showed suppression in the NF-κB rather than activation in the pathogenesis of Parkinson's disease by miR-7 (Choi *et al.*, 2014). Table 1 gives the differentially expressed miRNAs involved in mitochondrial pathways. At present there are many therapeutic strategies that are available. Inhibition of oncogenic miRNAs by antisense RNA and miRNAs mimics or viral encoded overexpression of tumor suppressor miRNAs (Sekar *et al.*, 2016a, 2016b; Bai *et al.*, 2019) are examples of the mentioned therapeutic strategy, but still we need to validate by high-throughput preclinical and clinical studies.

Conclusion

In general, we conclude that several miRNAs including miR-34a, miR-145, miR-146, miR-176, miR-181a, miR-762, miR-199a, miR-214, miR-93, and miR-96 play a vital role in many disease progressions or suppressions. The available pieces of evidence suggest a new framework for considering and understanding mitomiR as a novel biomarker in the mitochondrial dysfunctions linking it with many complex diseases. Mitochondrial dysfunction is also attributed to post-transcriptional modifications of targeted gene expression in noncommunicable diseases, including cardio vascular and neurodegenerative disorders. We already know the concept of miRNAs as biomarkers for various diseases that was explored thoroughly, but further, the analysis of miRNA profiles in serum, plasma, and blood cells linked with development and progression of mitochondrial dysfunctions may lead to novel therapeutic strategies. In addition, miRNAs may serve as a potential prognostic and diagnostic marker for mitochondrial linked diseases. Still, significant research endeavors have to be exercised on miRNAs that will determine the future use and clinical application. Nevertheless, the applicability of miRNAs in mitochondrial research remains elusive. The mentioned research findings suggest that miRNAs have a novel and important role in mitochondrial diseases/dysfunctions.

Disclosure Statement

No competing financial interests exist.

Funding Information

This work is not funded by any funding bodies.

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Received for publication August 12, 2019; received in revised form November 7, 2019; accepted November 20, 2019.