**Biological and clinical relevance of microRNAs in mitochondrial diseases/ dysfunctions**

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Abstract

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. 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 existing in sight of this disease and needs a new insight into molecular and signalling pathways for this disease. MicroRNAs (miRNAs) are small, endogenous, non- coding RNAs functions as a master regulator of gene expression. The evolution of miRNAs in the last 2 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 non communicable diseases. But, in the case of mitochondrial dysfunction in miRNAs the number of studies and investigations are comparatively less to 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, therapeutic target.

## 1. Introduction

To sustain life and to support organ functions, our body requires more than 90% of the 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 like Alzheimer’s disease, Parkinson’s disease (Grimm et al., 2016 ; Arun et al., 2016) cancer (Sotgia et al., 2011; Jezierska-Drutel et al., 2013) and majorly in cardiovascular diseases (Limongelli et al., 2012).

MicroRNAs (miRNAs) are single stranded, small, non coding 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 an enzyme RNase III Dicer to produce 22 nt mature miRNAs (Panagal et al., 2018). Generally, mature miRNAs can identify their cognate mRNA and bind its 3’ end of the untranslated region (UTR) for the post-transcriptional repression activity (Panagal et al., 2018; Panagal et al., 2018).

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, report suggesting that after translocation, mitomiRs can bind to the 3’- end of a mitochondrial gene, altering its regulation. MicroRNAs perform as anti-regulators of gene expression (Giuliani et al., 2017). Interestingly, there are so many miRNAs that plays an important role in the mitochondrial diseases and dysfunctions for example miR-122, miR-762, miR-217 etc (Wang et al., 2019; Yan et al., 2019., Tang et al., 2019).

The evolution of miRNAs in the last 2 decades emerged as a key regulator of gene expression that controls physiological, pathological, cellular, differentiation processes and metabolic homeostasis (Sekar et al., 2019; Sekar et al., 2016). miRNAs are a potential biomarker in both communicable and non communicable diseases. But, in the case of mitochondrial

dysfunction in miRNAs the number of studies and investigations are comparatively less to other diseases and dysfunctions. In this review, we have elaborated on the roles of microRNA in the mitochondrial diseases and dysfunctions.

## 2. 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 (Panagal et al., 2018; Panagal et al., 2018; Giuliani et al., 2017). Inspite of, miRNAs involved in several diseases and their role been clearly delineated (Sekar et al., 2019), up to our knowledge publications related to miRNAs in mitochondria and its related diseases is very less; we summarize below some of the research evidence from those published articles.

Recently Giuliani A et al 2017 illustrated the role of miRNAs on mitochondria in senescence. In that article, they explained miR-146 was translocated into mitochondria and alter the energetic, oxidative and inflammatory status of senescent cells, suggesting that miRNA-146 is involved in aging induced inflammation thereby reduce the aging rate and postpone 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. On the other hand, several miRNAs has been associated with cardiac remodelling by modulating key signalling elements in the myocardium. In particular, miR-195 has been identified as a molecule that down regulates the SIRT 3 expression by directly targeting its 3' UTR and alters the cardiac energy metabolism through elevated PDH acetylation levels and raised ATP synthase (Zhang et al., 2018).

A study by Koh E H, et al 2016 has reported on mitochondrial activity in human white adipocytes is regulated by the ubiquitin carrier protein 9/ microRNA- 30a axis. UBC-9 and miRNA- 30a exhibit an inverse expression in adipose tissue, and miRNA-30a 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 (Koh et al., 2016).

Wu Q 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-ß1. Suppression of miR-1224-5p hampers the progression of silica- induced fibrosis in vivo and TGF-ß1- 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 up regulated and conversely their target Bcl-2 being down- regulated. Interestingly, Bcl-2 an anti- oxidant, anti- apoptotic 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 microRNAs may play a regulatory role by regulating mitochondrial protein expressions (Rippo et al., 2014). Figure 1 shows the role of microRNA in mitochondria function/dysfunction.

Another miRNA, miR- 145 has been attributed in regulating mitochondrial apoptotic pathway in the heart challenged with oxidative stress. It is hypothesised that miR- 145 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 non coding RNAs such as miRNA act as a responsible gene regulator and has been involved in cellular signalling pathways. Yan K, et al 2019 reported on miR-762, a new miRNA in the mitochondrial dysfunction. miR-762 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, increased in reactive oxygen species- ROS levels, the decreased 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 (ND 2) 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 D, et al 2017 has mentioned about decreased mitochondrial function playing an important role in numerous pathologies including cardiomyopathy, cancer, neuro- muscular degeneration, Alzheimer’s disease and type-2 diabetes mellitus (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 has been upregulated during myocardial hypoxia and elevated in cardiac biopsies of heart failure patients and actively repress the PPARδ a well- known transcription factor in the regulation of mitochondrial metabolism. Interestingly from a therapeutic standpoint, in vivo silencing of miRNAs with specific antogomirs 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, 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 M et al 2017 on miR- 93, a hallmark miRNA in diabetic environment has been shown to be downregulated in diabetes mellitus. Additionally, 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 peroxisome proliferator activated receptor (α PPAR) (Galvan et al., 2017).

Interestingly, a study by Wen F et al 2018 on resistin levels which is associated with steatohepatitis and non- alcoholic fatty liver disease confirmed that miR-34a has been upregulated by resistin and mediated by CCAAT/enhancer-binding protein beta (C/EBPß). Furthermore, miR-34a inhibit 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 (AMPK) pathway in mitochondria (Wen et al., 2018).

Li K 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 (NRF-1) and mitochondrial transcription factor A (TFAM). In The same cells, miR- 144-3p overexpression significantly inhibited the protein expression of ß-amyloid precursor protein (APP). In the same study, noticeable raise in cellular ATP, cell viability and the relative copy number of mitochondrial DNA (mtDNA) was noted,

3uggesténg 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 (MMP) levels in human pulmonary artery smooth muscle cells (HPASMCs) suggesting that miR-138 promote proliferation and suppress mitochondrial depolarization of HPASMCs by targeting TASK-1gene (Liu et al., 2018).

Wang L, et al 2014 identified a microRNA that targets Glutathiïne peroxidise- 1 an important intracellular antioxidant enzyme that enzymatically quench hydrogen peroxide to water and limit its harmful enfects (GPx 1) and maintain redox homeostasis. They used quantitative real- time PCR (qPCR) which demonstrated the markedly upregulated expression of miR-181a in H2O2- treated H9C2 cells and the down regulation of miR-181a correlated with inhibition of $H_2O_2$ induced cellulav apoptosis, ROS production and increase in melondialdehyde
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A) levels. Their results suggested that miR- 181a plays an important role in regulating the mitochondrial apoptotic pathway in cardiomyocytes provoked by oxidative stress and also it is considered as a potential therapeutic target for the treatment nf oxidative stress- associated cardiovascular diseases (Wang et al., 2014). Figure 2 shows the microRNA regulation on mitochondrial apoptotic pathway.

An interesting spudy by Jeong H J et al 2013"elaborated on mitochonlrial dysfunction by impairment of insulin signalling in SK- Hep 1 cells via a reduction in the expression of IRS-1 3’ UTR. Uskng 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 signalling. 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 L et al 2013 found that mitochondrial uncoupling protein 2 (UCP2) was induced in$kidney tubular epithelial cells. In NRK- 52E cells, TGF- ß 1 remarkably induced UCP- 2 expression and the knockdown of UCP 2 mRNA largely abolished the effect of TGF- ß 1. Moreover, they found that the UCP 2 mRNA is a direct target of miR- 30e. Conversely, miR- 30e mimics significantly inhibit the TGF- ß 1, whereas

miR- 30e inhibitor imitates TGF- ß 1 effect on the NRK-52E cells. Thus, they conclude that the mitochondrial miR- 30/UCP2 axis has an important role in mediating TGF- ß 1- 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 above discussed studies, one can see the correlation between several miRNAs and mitochond2ia in various 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 via mitochondrial intervention in reversing the pathogenesis and protection against various metabolic conditions. From a therapeutic viewpoint, these miRNAs and their mimics show a promising ftture and opens new avenues in diseases managements 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.

## 3. Clinical Perspective and Future directions

MicroRNAs (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., 2016, Bai et al., 2019). miRNAs interact with the messenger RNAs (mRNAs) at the post transcriptional levels and regulate the gene expressions by either repression or degradation of the translation mechanisms. In general miRNAs considered being a key regulator for breast cancer progressions and readily detected in all kinds of body fluids including serum, blood, urine, semen, etc (Li et al., 2019, Humphries 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 potential impact of miRNAs as a biomarker for mitochondrial dysfunction and their interaction with surrounding molecular pathways (Li et al., 2016; Liu et al., 2018; Wang et al., 2014; Jeong et al., 2013; Jiang et al., 2013).

miRNAs that are present in the mitochondrial fraction and alters the mitochondrial function are called MitomiR (Srinivasan et al., 2015) . Among the reported miRNAs, miR-1291, miR-138, miR-150, miR-199a-3p, and miR-532-5p are involved to modify the expression of key

glycolytic enzymes, including glucose transporters (GLUTs) suggesting that mitochondrial glucose uptake can be modified by MitomiR (Srinivasan et al., 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 signalling pathways that are essential for regular mitochondrial function.

A review of Tomasetti M, et al 2014 illustrated that the modulation of miRNAs levels may provide a new therapeutic approach for the treatment of mitochondrial- related pathologies, including neoplastic diseases (Tomasetti et al., 2014). Interestingly, Kato M, 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 biomarker in both communicable and non communicable diseases (Sekar et al., 2016; Bai et al., 2019; Li et al., 2019; Humphries et al., 2019), On the other hand, in the case of mitochondrial dysfunction in miRNAs the number of studies and investigations are comparatively less to other diseases and dysfunctions. We still require more research to prove that miRNAs are vibrant prognostic, diagnostic and therapeutic biomarker for mitochondrial dysfunction. Surprisingly, Tomasetti M, et al 2014 summarizes the role of miR- 126 in the malignant mesothelioma (MM) H28 cell lines affect the mitochondrial energy metabolism, reduced mitochondrial respiration and promote the glycolysis. Furthermore, the above parameters resulted in suppression of MM tumour and miR-126 may act as therapeutic options for fatal neoplastic disease (Humphries et al., 2019). Another study by Choic DC et al 2014 also summarized on downregulation of relA , a component of NF- κB assosciated with miR-7. Their findings showed suppression in the nuclear factor-κB (NF-κB) rather than activation in the pathogenesis of Parkinson disease by miR-7(Choi et al., 2014). Table 1 shows 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 encodeced overexpression of tumour suppressor miRNAs (Sekar et al., 2016; Bai et al., 2019) are

examples of the above said therapeutic strategy, but still we need to have future validation by high throughput preclinical and clinical studies .

## 4. 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, miR- 96 play a vital role in many disease progressions or suppressions. The available evidences 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 expressions in non-communicable diseases including cardio vascular and neurodegenerative disorders. We already know the concept of miRNAs as biomarkers for various diseases which 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 endeavours has 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 above research findings suggest that miRNAs has a novel and important role in mitochondrial diseases/dysfunctions.

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