MitomiRs: their roles in mitochondria and importance in cancer cell metabolism

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Background. MicroRNAs (miRNAs) are short non-coding RNAs that play important roles in almost all biological pathways. They regulate post-transcriptional gene expression by binding to the 3' untranslated region (3'UTR) of messenger RNAs (mRNAs). MitomiRs are miRNAs of nuclear or mitochondrial origin that are localized in mitochondria and have a crucial role in regulation of mitochondrial function and metabolism. In eukaryotes, mitochondria are the major sites of oxidative metabolism of sugars, lipids, amino acids, and other bio-macromolecules. They are also the main sites of adenosine triphosphate (ATP) production.

Conclusions. In the review, we discuss the role of mitomiRs in mitochondria and introduce currently well studied mitomiRs, their target genes and functions. We also discuss their role in cancer initiation and progression through the regulation of miRNA expression in mitochondria. MitomiRs directly target key molecules such as transporters or enzymes in cell metabolism and regulate several oncogenic signaling pathways. They also play an important role in the Warburg effect, which is vital for cancer cells to maintain their proliferative potential. In addition, we discuss how they indirectly upregulate hexokinase 2 (HK2), an enzyme involved in glucose phosphorylation, and thus may affect energy metabolism in breast cancer cells. In tumor tissues such as breast cancer and head and neck tumors, the expression of one of the mitomiRs (miR-210) correlates with hypoxia gene signatures, suggesting a direct link between mitomiR expression and hypoxia in cancer. The miR-17/92 cluster has been shown to act as a key factor in metabolic reprogramming of tumors by regulating glycolytic and mitochondrial metabolism. This cluster is deregulated in B-cell lymphomas, B-cell chronic lymphocytic leukemia, acute myeloid leukemia, and T-cell lymphomas, and is particularly overexpressed in several other cancers. Based on the current knowledge, we can conclude that there is a large number of miRNAs present in mitochondria, termed mitomiR, and that they are important regulators of mitochondrial function. Therefore, mitomiRs are important players in the metabolism of cancer cells, which need to be further investigated in order to develop a potential new therapies for cancer.

Key words: microRNAs; mitomiR; mitochondria; cancer; cancer cell metabolism

Introduction

MicroRNAs (miRNAs) are short non-coding RNAs (ncRNAs) of ~18-25 nucleotides that are present in all eukaryotic cells and play important roles in almost all biological signaling pathways.1-4 Since the discovery of the first miRNA (lin-4) in C. elegans5, approximately 2000 miRNAs have been annotated in the human genome.6 Data from genomic studies show that most miRNAs are highly conserved, making them very interesting targets for studying various disease states.7 They regulate post-transcriptional gene expression by binding to the 3'UTR of messenger RNAs.8-14 A single miRNA
can regulate many mRNA targets, and conversely, a single mRNA target can be regulated by many miRNAs.\textsuperscript{15–17} Therefore, by regulating these fundamental target genes, miRNAs have been implicated in signaling pathways to modulate a large set of important biological processes such as cell proliferation\textsuperscript{2}, metastasis\textsuperscript{19}, apoptosis\textsuperscript{19}, senescence\textsuperscript{21}, differentiation\textsuperscript{25}, autophagy\textsuperscript{21}, and immune response\textsuperscript{22}. Moreover, miRNAs have been found to be dysregulated in many pathological conditions, such as neurodegenerative diseases\textsuperscript{23}, cardiovascular diseases\textsuperscript{24}, and cancer.\textsuperscript{25–28}

More recently, miRNAs have been found to be specifically present in mitochondria. These mitochondrial miRNAs were named “mitomiR”\textsuperscript{7,29–32} Most of them have a nuclear origin, but some mitomiRs originate from mRNA molecules derived from the mitochondrion genome. The association of mitomiRs with mitochondria is species- and cell type-specific.\textsuperscript{7,33} They have been found in mitochondria in various tissues and cells and are thought to have different thermodynamic properties than miRNAs.\textsuperscript{7,24} Mitochondria have a discrete and unique pool of mitomiRs, which has been demonstrated with various experiments.\textsuperscript{29}

For the first time, in 2011, Barrey and co-workers demonstrated the presence of pre-miRNAs (precursor-miRNAs) in mitochondria and postulated that some pre-miRNA sequences could be processed into mature miRNAs that could immediately become active on mitochondrial transcripts or exported to the cytosol to disrupt genomic mRNA.\textsuperscript{35} Barrey’s group screened for 742 miRNAs using qRT-PCR and showed that 243 miRNAs had significant expression in mitochondrial RNA samples isolated from human myotubes by \textit{in situ} hybridization. This study was the first to provide evidence that pre-miRNAs can be localized in mitochondria. Subsequently, a number of studies have identified “signatures” of miRNAs localized to mitochondria through various experimental approaches. Mercer \textit{et al.}\textsuperscript{35} examined the human mitochondrial transcriptome and demonstrated that 3 miRNAs (miR-146a, miR-103, and miR-16) have quite high expression in the intermembrane region compared to the matrix. Latronico and Condorelli\textsuperscript{36} found 15 nuclear-encoded miRNAs in mitochondria isolated from rat liver, 20 miRNAs from mouse liver mitochondria, and 13 miRNAs from HeLa cells (isolated from human cervical cancer) by microarray. Some other groups identified novel mitomiRs from HEK293 cells (isolated from human embryonic kidneys)\textsuperscript{37}, 143B cells (isolated from human bone marrow)\textsuperscript{38}, mouse heart\textsuperscript{39} and HeLa cells.\textsuperscript{37,40}

MitomiRs have been shown to be important regulators of mitochondrial function.\textsuperscript{35,38,41} The regulation of mitochondria by mitomiRs influences the development of many diseases caused by mitochondrial dysfunction, which is responsible for the pathophysiology of numerous diseases, such as cardiovascular and neurodegenerative diseases, diabetes, obesity, and cancer.\textsuperscript{42}

In the first part of this review article, we describe the biosynthesis of mitomiRs and the transport mechanisms from mitomiRs to mitochondria. The next part is dedicated to the role of these small molecules in mitochondria and the presentation of some important mitomiRs, their target genes and functions. In the last part of the review, we discuss the functions of mitomiRs in cancer cell metabolism and introduced mitomiRs in the context of cancer.

\section*{Biosynthesis of miRNA/mitomiRs}

Most miRNAs/mitomiRs are produced via the canonical biosynthetic pathway, which involves transcription by RNA polymerase II (Pol II) to produce a primary transcript (pri-miRNA/mitomiR). The primary transcript is first cleaved in the nucleus by the nuclear heterodimer Drosha/DGCR8 (DiGeorge syndrome chromosomal region 8), which cleaves the pri-miRNA/mitomiR and produces a pre-miRNA/mitomiR with a hairpin structure that is much more stable than the pri-miRNA/ mitomiR due to its characteristic hairpin loop structure.\textsuperscript{43} Exportin 5 (EXP5) and GTP-binding nuclear protein (RANGTP) then form a transport machinery to export the pre-miRNA from the nucleus to the cytoplasm. After export to the cytoplasm, the pre-miRNA/mitomiR is further cleaved by the enzyme Dicer to form a double-stranded RNA (dsRNA) duplex (Figure 1). Only a single strand of the dsRNA duplex forms the mature miRNA/mitomiR and is incorporated into the RNA-induced silencing complex (RISC), which directs the binding of Argonaute (AGO) proteins in the RISC to the 3'UTR of the target mRNA to either repress protein translation or promote mRNA degradation.\textsuperscript{43–45} After incorporation into RISC, mature miRNA/mitomiRs are transported into mitochondria, back to the nucleus by importin 8 (IPO-8) or extracellular environment (Figure 1).\textsuperscript{36,47}

In addition to the canonical miRNAs/mitomiRs biosynthesis pathway, there are also non-canonical, Drosha/DGCR8-independent and Dicer-independent biosynthesis pathways. Prominent
classes of Drosha/DGCR8-independent miRNAs/mitomiRs are the “mirtrons” derived from introns that, once spliced, function as pre-miRNAs and thus do not require cleavage by Drosha/DGCR8 and can be immediately exported to the cytoplasm for processing by Dicer. MiRNAs/mitomiRs can also be processed from hairpins generated directly by Pol II at specific transcription start sites. These pre-miRNAs are capped and exported via the exportin 1 (EXP1) pathway. The Dicer-independent miRNAs/mitomiRs biosynthesis pathway involves the unusually short hairpin of miR-451, which is directly cleaved by argonaute 2 (AGO2).

**MitomiRs transport to mitochondria**

The discovery of mitomiRs raised the question of elucidating the underlying molecular mechanisms of their transport into mitochondria. Due to their size and charged nature, mitomiRs are unlikely to cross membranes under their own power. The molecular mechanisms of mitomiR transport into mitochondria may vary between species and are not well understood. Some proposals have been published on AGO2 as a potential mitomiR import protein. Due to its RNA-binding ability and dual localization in the cytosol and mitochondria, AGO2 might be involved in the trafficking of mitomiRs. Shepherd et al. showed that the exoribonuclease polyribonucleotide nucleotidyltransferase (PNPT1/ PNPase) has a major role in the import of mitomiRs. Therefore, PNPase could be part of an alternative, AGO2-independent, uptake pathway of mitochondrial miRNA. Furthermore, a possible mechanism could involve the voltage-dependent anion-selective channel protein (VDAC). Several studies have suggested that the instability of RISC in the

![Diagram of canonical biosynthesis of miRNAs/mitomiRs](image-url)
cytoplasm promotes miRNA translocation to mitochondria, but the molecular components that facilitate this translocation process are not fully understood. Furthermore, the concept that mammalian mitochondria can import cytosolic ncRNAs may facilitate research in another exciting area, long ncRNAs. Clearly, these translocation mechanisms and the identification of pathway components for mitochondrial targeting require further studies.7

Roles of mitomiRs in mitochondria

Mitochondria are semi-autonomous cell organelles with their own DNA (mtDNA) encoding 22 tRNAs, 2 rRNAs, and 13 polypeptides. These polypeptides and those encoded by nuclear genes, form 4 protein complexes of the electron transport chain (ETC). Mitochondria are constantly dividing and fusing, and the balance between mitochondrial fission and fusion influences mitochondrial morphology, whose dynamics and turnover are critical for cellular homeostasis and differentiation.50 Several proteins are involved in the regulation of mitochondrial dynamics. Deregulation of mitochondrial dynamics is not only associated with deregulation of mitochondrial function, but is also closely related to several biological processes such as proliferation, cell death, apoptosis and production of reactive oxygen species (ROS), since mitochondria are the major sites of oxidative metabolism of sugars, lipids, amino acids and ATP production.1,51–53

It’s also worth noting that the mitochondrial matrix has its own set of environmental variables. Because of its thioester bond, acetyl-coenzyme A (acetyl-CoA) is a very abundant metabolite in mitochondria and functions as a powerful acetylation reagent. Protein lysine acetylation and succinylation are caused by acetyl-CoA and mitochondrial matrix pH concentrations. Non-enzymatic acetylation occurs often in mitochondria.54 The most of mitochondrial proteins have acetyl groups, which is consistent with this hypothesis. Non-enzymatic acetylation of RNA molecules, including miRNAs, is a logical possibility for mitochondrial modification. An acetyl group covalently attached to a miRNA might change its mRNA recognition behavior. If it happens at the 2 OH group of ribose needed for the cleavage process, it could inhibit spontaneous bond cleavage and therefore increase the half-life of mRNA. Furthermore, post-transcriptional alterations can result in structural changes as well as changed interactions with other RNA molecules or proteins.56

As stated, mitomiRs are regulators of mitochondrial function, as shown in the following examples. In silico analysis identified miR-378, miR-24, and miR-23b in liver mitochondria (Table 1) and these mitomiRs have been shown to regulate systemic energy homeostasis, oxidative capacity, ROS, and mitochondrial lipid metabolism.35,57–62 Several reports have indicated that miRNAs such as miR-1291, miR-138, miR-150, miR-199a, and miR-532-5p can alter the expression of some important glycolytic enzymes (Table 1).44–47 miR-29a, miR-29b and miR-124 (Table 1) regulate the expression of monocarboxylate transporter 1 (SLC16A1) in pancreatic beta cells.71 miR-33a/b has been shown to regulate lipid metabolism by targeting the cholesterol transporter ATP-binding cassette transporter (ABCA1).72 miR-143 and miR-24 have also been shown to regulate mitochondrial lipid metabolism (Table 1).73,74 On the other hand, miR-204 accelerates fatty acid oxidation by inhibiting acetyl-coenzyme A carboxylase (ACC).75 Ahmad et al. (2011) showed that miR-200 is associated with the regulation of phosphoglucone isomerase (PGI), which is an important factor in glycolysis and glucogenesis. Overexpression of miR-338 leads to downregulation of the protein level of cytochrome c oxidase IV and reduces mitochondrial oxygen consumption and ATP production.77,78 Similarly, overexpression of miR-181c decreases mt-COX1 protein and causes remodeling of the complex IV (in vitro) and a dysfunctional complex IV (in vivo), along with increased production of ROS. It has also been reported that miR-210 modulates the function of the complex IV by targeting the nuclear-encoded mRNA, COX10.80,81 It has also been reported that miR-15b, miR-16, miR-195 and miR-338 (Table 1) regulate ATP production by targeting several nuclear genes that play important roles in ETC.77,83 miR-101-3p regulates the expression of ATP synthase subunit beta (ATP5B) in ETC (Table 1).84 In addition, miR-210-5p reduces the expression of iron-sulfur cluster assembly enzyme (ISCU) under hypoxic conditions, which affects the proteins containing iron-sulfur clusters (Fe-S).85 It has also been reported that miR-29a-3p is involved in β-oxidation of lipids (Table 1) and that miR-19b negatively regulates mitochondrial fusion by downregulating mitofusin 1 (MFN1).87

The microRNAs listed in Table 1 significantly affect mitochondrial regulation and function, which is why they are classified in the group of mitomiRs, which are crucial regulatory molecules.
### TABLE 1. Summary of microRNAs and their roles in mitochondria

| miR   | accession number | Target genes     | Gene accession number | Function                  | Functional pathway                  | Location                  | Species     | References                |
|-------|------------------|------------------|-----------------------|---------------------------|--------------------------------------|---------------------------|-------------|---------------------------|
| miR-378 | MI0000795         | Crat             | ENSMUSG00000026553    | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in liver cells | Mouse       | Carre et al., 2012⁶⁹     |
| miR-24  | MI0000080         | H2ax             | ENSMUSG000000049932   | Downregulation            | Insulin signaling pathway            | Mitochondria in liver cells | Human       | Jeong et al., 2017⁶⁸     |
| miR-23b | MI0000439         | GLS              | ENSG00000115419       | Downregulation            | Glutamine metabolism                | LMitochondria in liver cells | Human       | Gao et al., 2009⁶⁷     |
| miR-129 | MI00006333        | SLCA2A, CPT1C, ESRRA, ASS1, GLUT1 | ENSG00000117394, ENSG00000169169, ENSG00000173153, ENSG00000130707, ENSG0000017594 | Downregulation | Mitochondrial oxidative metabolism | Mitochondria in liver cells | Human       | Yamasaki et al., 2013; Chen et al., 2020; Yu et al., 2020⁶⁵,⁶⁶   |
| miR-138 | MI0000455         | PDK1             | ENSG00000152556       | Downregulation            | Glucose metabolism                  | Mitochondria in liver cells | Human       | Zhu et al., 2017⁷⁴     |
| miR-150 | MI0000920         | Slc2a4           | ENSRNQG0000017226     | Downregulation            | Metabolism                           | Mitochondria in liver cells | Human       | Hu et al., 2009⁷²        |
| miR-199a | MI0000941         | Slc2a4, Hk2      | ENSRNQG0000017226, ENSRNNQRG00000611156 | Upregulation | Expression of glucose transporters | Mitochondria in muscle cells | Rat         | Esteses et al., 2018; Yan et al., 2014; Guo et al., 2015⁶⁷,⁷⁰   |
| miR-532-3p | MI0006154       | Slc2a4, Hk2      | ENSRNQG0000017226, ENSRNNQRG00000611156 | Upregulation | Expression of glucose transporters | Mitochondria in muscle cells | Rat         | Esteses et al., 2018⁷⁰   |
| miR-29a | MI0000576         | Slc16a1          | ENSMUSG00000032902    | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in pancreatic beta-cells | Mouse       | Pullen et al., 2011⁷¹   |
| miR-29b | MI0000143         | Slc16a1          | ENSMUSG00000032902    | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in pancreatic beta-cells | Mouse       | Pullen et al., 2011⁷¹   |
| miR-124 | MI0000716         | Slc16a1          | ENSMUSG00000032902    | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in pancreatic beta-cells | Mouse       | Pullen et al., 2011⁷¹   |
| miR-33a/b | MI00002684, a-MI00007603 | CROT, CPT1A, HADHB, PRKAA1, ABCA1, SREBF1, FASN, ALCY, ACACA | ENSANAG00000028065, ENSANAG00000017354, ENSANAG00000027802, ENSANAG00000032687, ENSANAG00000033387, ENSANAG00000017354, ENSANAG00000032687, ENSANAG00000033387, ENSANAG00000032555, ENSANAG00000036009, ENSANAG00000032523 | Downregulation | Lipid metabolism | Mitochondria in liver cells | Monkey      | Rayner et al., 2011⁷⁵   |
| miR-143 | MI0000916         | Map3k5           | ENSRNQG00000007926    | Downregulation            | Adipogenesis                         | Mitochondria in adipose cells | Rat         | Chen et al., 2014⁷³     |
| miR-204 | MI0000284         | ACACB            | ENSG00000075655       | Downregulation            | Lipid metabolism                     | Mitochondria in adipose cells | Human       | Civelek et al., 2013⁷⁵   |
| miR-200 | MI0000737         | ZEB1, ZEB2       | ENSG00000148516, ENSG00000169554 | Upregulation | Lipid metabolism | Mitochondria in breast cells | Human       | Ahmad et al., 2011⁷⁶   |
| miR-338 | MI0000618         | COXIV            | ENSRNQG00000007827    | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in neural cells | Rat         | Aschrafi et al., 2008⁷⁷   |
| miR-181c | MI0000924         | COX1             | ENSRNQG000000034234   | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in cardiac cells | Rat         | Das et al., 2012⁷⁸     |
| miR-210 | MI0000268         | BCUC             | ENSG00000136003       | Downregulation            | Mitochondrial oxidative metabolism   | Mitochondria in placenta | Human       | Colleoni et al., 2013; Qiao et al., 2013⁷¹,⁷²   |
| miR-15b | MI0000845         | At2, Bc2         | ENSRQG00000021010, ENSRNNQG00000022791 | Downregulation | ATP production | Mitochondria in cardiac cells | Rat         | Nishi et al., 2010⁶⁸     |
| miR-16 | MI0000844         | Bc1, At2         | ENSRQG00000021010, ENSRQG00000021010 | Downregulation | ATP production | Mitochondria in cardiac cells | Rat         | Nishi et al., 2010⁶⁸     |
| miR-195 | MI0000939         | At2              | ENSRQG00000021010     | Downregulation            | ATP production                       | Mitochondria in liver cells | Mouse       | Kurtz et al., 2014⁷⁴     |
| miR-29a-3p | MI0000576       | Foxa2            | ENSMUSG00000037025    | Upregulation | Lipid metabolism | Mitochondria in liver cells | Mouse       | Kurtz et al., 2014⁷⁴     |
| miR-19b | MI0000074         | MPP1             | ENSG00000171109       | Downregulation            | Apoptosis                             | Mitochondria in bone cells | Human       | Li et al., 2014⁷⁴       |
| miR-101-3p | MI0000103       | ATP5B            | ENSG00000110955      | Silencing                 | Mitochondrial oxidative metabolism   | Mitochondria in HeLa cells | Human       | Zheng et al., 2011⁷⁵   |
of mitochondrial function and regulation of metabolism. In the figures (Figure 2 and Figure 3), we have shown how these mitomiRs are linked to their target genes in primates (Figure 2) and rodents (Figure 3).

In primates, there is no regulation of the same genes by different mitomiRs from Table 1 (Figure 2). Moreover, most mitomiRs target one gene and only a few mitomiRs target a larger number of genes and in most cases mitomiRs downregulate genes.

In contrast to primates, in rodents, some genes are regulated by different mitomiRs (Figure 3). The mitomiRs miR-15b and miR-16 both regulate the Arl2 gene, which is a nucleotide-binding gene, and the Bcl2 gene, which regulates apoptosis. In addition, the mitomiRs miR-199a and miR-532-5p both regulate the Hk2 gene, which has an important function in regulating glucose metabolism, and the Slc2a4 gene, which is a glucose transmembrane transporter. It can be concluded that there is a greater overlap of mitomiRs in rodents than in primates. In most cases, mitomiRs downregulate genes.

From the figures (Figure 2 and Figure 3), we can summarize that some mitomiRs and their target genes are related in primates and rodents. MitomiR miR-199a regulates the same gene in both primates and rodents (Figure 3), the gene Hk2, which has an important function in regulating glucose metabolism. MiR-143 regulates the same gene MAP2K5 (Figure 3), which has an important

FIGURE 2. The network of the mitomiRs and their target genes (grey rectangle) in primates (data from Table 1). Blue arrows present downregulation, green arrows present upregulation and black T-line present silencing. Purple octagon shape presents monkey miRNA and cyan hexagon presents human miRNAs (figure constructed with Cytoscape Network Data Integration, Analysis, and Visualization in a Box V3.8.2).
function in signal cascade involved in growth factor stimulated cell proliferation and muscle cell differentiation.

**MitomiRs in cancer**

Traditional cancer traits include ten biological capabilities gained during the multistage development of human tumors. These ten traditional cancer traits include resistance to cell death, induction of angiogenesis, maintenance of proliferative signaling, evasion of growth suppressors, activation of invasion and metastasis, facilitation of replicative immortality, altered metabolism, evasion of destruction by the immune system, tumor-promoting inflammation, and genome instability (Figure 4).

An important feature of cancer is the presence of the Warburg effect. Under aerobic conditions, normal cells generate ATP primarily in the mitochondrial oxidative phosphorylation process (OXPHOS), which utilizes the products of glycolysis and the Krebs cycle. Under anaerobic conditions, relatively little pyruvate, the end product of glycolysis, is added to the Krebs cycle and is instead converted to lactate. However, this metabolic conversion of glucose appears to be energetically detrimental. In tumor cells, ATP deficiency can be compensated to some extent by upregulation of glycolysis. Interestingly, it has been observed that many cancer cells prefer glycolysis over OXPHOS even in the presence of an adequate amount of oxygen. This abnormal energy metabolism is known as the Warburg effect. Reduced OXPHOS and enhanced aerobic glycolysis are the main manifestations of reprogramming of glucose metabolism in tumor cells. Albeit the specific causes and utilitarian outcomes of this metabolic switch are as yet unclear, there is a developing agreement that the impact of Warburg effect is certifiably not an inconsequential result of carcinogenesis, yet is imperative for cancer cells to keep up with their proliferative potential and is driven by a few elements.

It has been confirmed that abnormal expression of mitomiRs in mitochondria is related to the occurrence of cancer features. Moreover, mitomiRs play an essential role in the control of cancer cell metabolism by regulating mRNA expression. They regulate several oncogenic signaling pathways and...
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target key transporters or enzymes in cellular metabolism. In addition, they may have a function as tumor suppressors that inhibit tumor cell proliferation or as oncogenes that induce tumorigenesis. MitomiRs can be isolated from any tissue or body fluid of any organism to study the level of expression in the organism in a diseased state, and thus can function as novel prognostic and predictive biomarkers.

The first evidence of miRNA involvement in human cancers was provided in a study of chronic lymphocytic leukemia (CLL). MiR-15a and miR-16-1 localized to 13q14 were reported to be frequently deleted and/or reduced in patients with B-cell chronic lymphocytic leukemia. This finding provided the first evidence that miRNAs may be involved in the pathogenesis of human cancers, as deletion of chromosome 13q14 resulted in the loss of these two miRNAs. MiR-15a induces apoptosis by regulating mitochondrial function and affecting the activity of Bcl-2 and Mcl-1 in human (Table 2). In addition, miR-15a causes mitochondrial dysfunction, leading to the release of cytochrome c into the cytoplasm and depletion of mitochondrial membrane potential. MiR-15a and miR-16a have been shown to be ATP modulators correlated with

FIGURE 4. Traditional cancer traits.

Deregulating cellular energetics

Sustaining proliferative signaling

Avoiding growth suppressors

Enabling replicative immortality

Resisting cell death

Inducing angiogenesis

Tumor-promoting inflammation

Activating invasion and metastasis

Genome instability
TABLE 2. Summary of mitomiRs with roles in cancer

| miR   | miR accession number | Target genes | Gene accession number | Function   | Functional pathway                                      | Type of cancer                 | Species | References                                      |
|-------|----------------------|--------------|-----------------------|------------|--------------------------------------------------------|-------------------------------|---------|-------------------------------------------------|
| miR-210 | MIO0000286           | HIF-1        | ENSG00000258777       | Upregulation | Hypoxia                                                | Breast cancer, neck and head cancer, lung cancer | Human   | Qin et al., 2014; Gee et al., 2010; Puissegur et al., 2011 |
|       |                      | ISCU         | ENSG00000136000       | Upregulation |                                                        |                               |         |                                                 |
|       |                      | COX10        | ENSG00000006695       | Upregulation |                                                        |                               |         |                                                 |
|       |                      | SDHD         | ENSG00000204370       | Upregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFA4       | ENSG00000189043       | Upregulation |                                                        |                               |         |                                                 |
| miR-200a | MIO0000342        | TFAM         | ENSG00000108034       | Downregulation | Mitochondrial biogenesis, cancer metabolism            | Breast cancer                 | Human   | Yao et al., 2014                               |
| miR-155 | MIO0000681          | HK2          | ENSG00000159999       | Upregulation | Glucose phosphorylation                                | Breast cancer                 | Human   | Fang et al., 2012; Jiang et al., 2012          |
| miR-124 | MIO0000443          | PKM          | ENSG00000067225       | Upregulation | Glucose metabolism                                     | Colorectal cancer             | Human   | Sun et al., 2012                               |
| miR-137 | MIO0000454          | PKM          | ENSG00000067225       | Upregulation | Glucose metabolism                                     | Colorectal cancer             | Human   | Sun et al., 2012                               |
| miR-340 | MIO0000802          | PKM          | ENSG00000067225       | Upregulation | Glucose metabolism                                     | Colorectal cancer             | Human   | Sun et al., 2012                               |
| miR-326 | MIO0000808          | PKM2         | ENSG00000169043       | Downregulation | Mitogen-activated protein kinase (MAPK) signaling pathway | Gastric cancer, cervical cancer | Human   | Mi et al., 2017; Zhuang et al., 2017          |
| miR-181-5p | MIMAT0000256      | RASSF6       | ENSG00000169435       | Downregulation | Inflammation, angiogenesis                              | Breast cancer cells           | Human   | Mogilysynskaya and Rigoutsos, 2013            |
|       |                      | INPP5A       | ENSG00000068383       | Downregulation |                                                        |                               |         |                                                 |
| miR-92a-1 | MIO000093         | BCL2L11      | ENSG00000153094       | Downregulation | Apoptosis                                               | B-cell chronic lymphocytic leukemia | Human   | Gao et al., 2010                               |
| miR-126 | MIO0000471          | PK3R2        | ENSG00000105647       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | PLK2         | ENSG00000260410       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | EGFL7        | ENSG00000172889       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | CRK          | ENSG00000167193       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | ADAM9        | ENSG00000168615       | Downregulation |                                                        |                               |         |                                                 |
| miR-15a | MIO000069           | HOXA9        | ENSG00000078399       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | IR51         | ENSG00000169047       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | ZC3H10       | ENSG00000242080       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | SLC7A5       | ENSG00000103257       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | VEGFA        | ENSG00000150630       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | MMP7         | ENSG00000137673       | Downregulation |                                                        |                               |         |                                                 |
| miR-16a | MIO000070           | BCL-2        | ENSG00000171791       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | MCL-1        | ENSG00000143384       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | COX42        | ENSG00000131055       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | COX4A2       | ENSG00000156885       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFB7       | ENSG00000099795       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFV1       | ENSG00000167792       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFS4       | ENSG00000164258       | Downregulation |                                                        |                               |         |                                                 |
| miR-16b | MIO000070           | COX42        | ENSG00000131055       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | COX4A2       | ENSG00000156885       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFB7       | ENSG00000099795       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFV1       | ENSG00000167792       | Downregulation |                                                        |                               |         |                                                 |
|       |                      | NDUFS4       | ENSG00000164258       | Downregulation |                                                        |                               |         |                                                 |
Hypoxia has previously been related to altered mitomiR expression, with hypoxia-regulated mitomiR being found to play a key role in cell survival in oxygen-depleted settings. MiR-210 is one of the mitomiRs that is continuously increased in normal and transformed cells during hypoxia, suggesting that miR-210 plays a role in cells’ adaptive response to hypoxia. MiR-210 expression corresponds with hypoxia gene signatures in tumor tissues such as breast and head and neck cancers, demonstrating a direct connection between miR-210 expression and hypoxia in cancer. MiR-210 has been researched extensively and has a number of functionally significant targets in cell cycle control, cell survival, differentiation, angiogenesis, and metabolism. Cell metabolism switches from mitochondrial OXPHOS to glycolysis under hypoxic environments. HIF-1, a hypoxia-inducible factor that upregulates the expression of most glycolytic enzymes as well as pyruvate dehydrogenase kinase while downregulating mitochondrial respiration, plays a key role in this action. Previous research has looked into how miR-210 regulates mitochondrial metabolism under hypoxia. MiR-210 target iron-sulfur cluster assembly proteins (ISCU1/2) and inhibit the activity of iron-sulfur proteins that govern mitochondrial metabolism, such as complex I and aconitase, resulting in lower OXPHOS. It acts directly on cytochrome c oxidase assembly factor heme A:cytochrome c oxidase II (AcoXII), succinate dehydrogenase complex subunit D (SDHD), and NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4 (NDUFA4) in regulating mitochondrial activity. Another study found an abnormal mitochondrial phenotype in A549 lung cells overexpressing miR-210, and mRNA expression profile analysis connecting miR-210 to mitochondrial dysfunction. Interestingly, HIF is rapidly destroyed upon reoxygenation of hypoxic cells due to miR-210’s high stability, whereas miR-210 stays stable to maintain the glycolytic phenotype. Under normal conditions, this slows mitochondrial respiration and enhances glycolysis in H28 cells, associated with IRS1 modulate ATP-citrate lyase de-regulation. This leads to an increase in ATP and citrate production which is linked with reducing Akt signaling and inhibiting cytosolic sequestration of Forkhead box O1 (FoxO1), which promote the expression of genes involved in gluconeogenesis and oxidative stress defense.

Several studies reported that miR-126 has an important role in different human cancers (Table 2) such as breast, lung, gastric cancers, melanoma cancer and acute leukaemia. Tomasetti et al. reported that miR-126 affects mitochondrial energy metabolism, resulting in malignant mesothelioma tumor suppression. This mitomiR reduce mitochondrial respiration and promote glycolysis in H28 cells, associated with IRS1 modulate ATP-citrate lyase de-regulation. This leads to an increase in ATP and citrate production which is linked with reducing Akt signaling and inhibiting cytosolic sequestration of Forkhead box O1 (FoxO1), which promote the expression of genes involved in gluconeogenesis and oxidative stress defense.
transcription factor activity is required for mtDNA replication and transcription. In addition to its function in replication and transcription, the presence of TFAM is necessary for mtDNA maintenance. It has also been implicated as a primary architectural protein of the mitochondrial genome by packaging mtDNA. In addition, TFAM expression has been reported to be involved in tumor progression, cancer cell growth, and chemoresistance.

Regarding the role of miRNAs in cancer and metabolism, the miR-17/92 cluster is one of the best characterized oncogenic miRNAs. This cluster is also known as oncomiR-1, and there is growing evidence of its oncogenic potential. It has been shown that miR-17/92 suppresses apoptosis and was originally found amplified in B-cell lymphomas, where ectopically overexpressed truncated versions lacking miR-92a-1 were shown to possess oncogenic properties. The MiR-17/92 cluster is deregulated in B-cell lymphomas, T-cell lymphomas, B-cell chronic lymphocytic leukemia, and acute myeloid leukemia. This cluster is particularly overexpressed in several other cancers, including osteosarcoma, neuroblastoma, cervical, pancreatic, breast, lung, colorectal, ovarian, kidney, and liver cancers. Izreig et al. reported that this miRNA cluster is a key factor in metabolic reprogramming of tumors. If oncomiR-1 is absent in Myc+ tumor cells, there is a global decrease in glycolytic and mitochondrial metabolism. If increased oncomiR-1 expression is present, this is sufficient for increased nutrient utilization by tumor cells. Deletion of miR-17/92 promoted changes in gene expression in Myc+ lymphoma which results in global decrease in metabolic pathways including glycolysis, the Krebs cycle, components of the electron transfer chain, amino acid metabolism, the pentose phosphate pathway, serine biosynthesis and nucleotide biosynthesis.

Conclusions

MiRNAs have been found in the mitochondria of many cell types, as shown by an increasing number of studies and they were named mitomiRs. In general, mitomiR populations differ in various tissues and under different pathological circumstances, implying that mitomiR populations are regulated by mechanisms that remain to be discovered. Based on the available information, we can deduce that there are a significant number of miRNAs which are present in mitochondria.

In our review, we have shown that various mitomiRs play a role in the initiation and progression of cancer via the regulation of mitochondria. They are involved in the Warburg effect, which is necessary for cancer cells to maintain their proliferative capacity. MitomiRs also upregulate HK2, a glucose phosphorylation enzyme, in an indirect manner, which may impact energy consumption in breast cancer cells. Expression of one of the mitomiRs (miR-210) corresponds with hypoxia gene signatures in tumor tissues such as breast cancer and head and neck cancers, demonstrating a clear connection between mitomiR expression and hypoxia in cancer. MiRNAs have emerged in the last decade as key regulators in cancer-related processes and are classified as either oncogenic or tumor suppressive miRNAs. The miR-17/92 cluster was first discovered to be amplified in diffuse cell lymphoma and B-cell lymphoma. This mitomiR cluster suppresses apoptosis and may act as an oncogene in B-cell lymphomas, B-cell chronic lymphocytic leukemia, acute myeloid leukemia, and T-cell lymphomas. It is also overexpressed in numerous other malignancies. This cluster is a key factor in metabolic reprogramming of tumors. Tumor-targeting treatments based on mitomiRs are emerging as a novel diagnostic and therapeutic tool.

Future perspectives

We have shown that mitomiRs are important players in mitochondria of cancer cell that need to be further investigated to develop a new potential therapies for cancer. Numerous studies that have been published in recent years give promising predictions that mitomiRs will receive more attention in the context of their role in cancer as possible biomarkers or targets for treatment.

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