

## MINI-REVIEW

# Role of MicroRNAs in the Warburg Effect and Mitochondrial Metabolism in Cancer

Hui-Jin Li<sup>1</sup>, Wei Chen<sup>2\*</sup>

### Abstract

Metabolism lies at the heart of cell biology. The metabolism of cancer cells is significantly different from that of their normal counterparts during tumorigenesis and progression. Elevated glucose metabolism is one of the hallmarks of cancer cells, even under aerobic conditions. The Warburg effect not only allows cancer cells to meet their high energy demands and supply biological materials for anabolic processes including nucleotide and lipid synthesis, but it also minimizes reactive oxygen species production in mitochondria, thereby providing a growth advantage for tumors. Indeed, the mitochondria also play a more essential role in tumor development. As information about the numerous microRNAs has emerged, the importance of metabolic phenotypes mediated by microRNAs in cancer is being increasingly emphasized. However, the consequences of dysregulation of Warburg effect and mitochondrial metabolism modulated by microRNAs in tumor initiation and progression are still largely unclear.

**Keywords:** Cancer - microRNAs - Warburg effect - mitochondria - metabolism

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### Introduction

Obtaining sufficient energy is a critical issue for cells to survive. In contrast to normal counterparts, most cancer cells rely on aerobic glycolysis, a metabolic phenotype referred as the Warburg effect (Gatenby et al., 2004). A shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis is a unique biochemical characteristic of cancer cells (Hsu et al., 2008). This altered response is required to provide sufficient amounts of metabolic intermediates for cell anabolic phase (Lunt et al., 2011; Maria et al., 2013) (Figure 1). There is still controversial in the cancer metabolism, because mitochondria are still play a vital role in energy production in cancer.

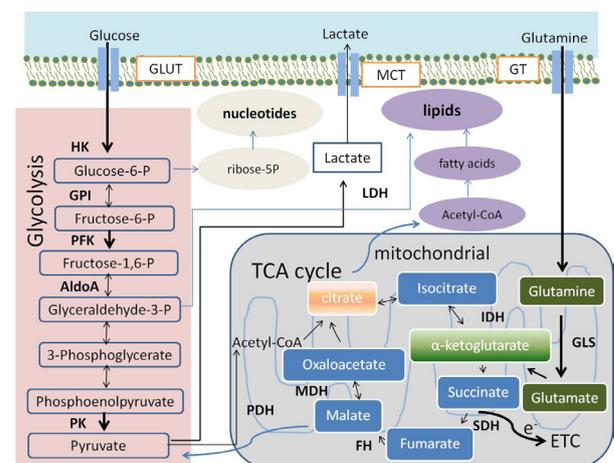
MicroRNAs regulate gene expression at the post-transcriptional level, either by causing target mRNAs degradation or by suppression of target gene translation or by upregulation of target mRNAs (Gigli et al., 2013). There is increasing evidence that a specific miRNA often regulates several target genes and one gene may be modulated by various miRNAs (Jackson et al., 2003). miRNAs are now considered a novel class of essential gene regulators for development and physiological processes (Ma et al., 2008).

Cancer cell metabolism is a multistep process controlled by some aberrant expression of both coding and non-coding gene. Recent studies have demonstrated that miRNAs play very critical roles in energy metabolism (Rottiers et al., 2012). The expression of a large number of oncogenes and tumor suppressor genes is regulated

by miRNAs. miRNAs regulate several key enzymes and signaling hubs that cause alterations in tumor development (Singh et al., 2012). The complexity of miRNAs regulated cancer metabolism is only just beginning to understand for cancer researchers. Hence, in this review, we will focus on the importance of miRNAs on Warburg effect and mitochondrial metabolism in cancer.

### Expression of microRNAs in human cancer

miRNAs play key roles in the development of human cancer, and expression profiles in human carcinoma



**Figure 1. Metabolic Processes and Key Players in Cell Energy Supply**

<sup>1</sup>Center for Translational Medicine, <sup>2</sup>Clinical Laboratory, The First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xian, China \*For correspondence: chenwei2011xjtu@gmail.com

initiation, progression and prognosis (Volinia et al., 2013). There are over 1000 human miRNAs, and these miRNAs frequently are associated with tumor progression (You et al., 2012). The first evidence of the involvement of miRNAs in human cancer emanating from studies on chronic lymphocytic leukemia (CLL) by Croce's group. They reported that miR-15a and miR-16-1, which are deleted in human CLL samples (Iorio et al., 2012). Several studies have demonstrated that the alterations in expression of miRNAs contribute to human malignancies, including the program of initiation, development and metabolic reprogramming in human cancer (Croce et al., 2009; Garzon et al., 2009; Anaya-Ruiz et al., 2013; Li et al., 2013; Qi et al., 2013).

### Regulation of key enzymes of Warburg effect by miRNAs

Many cancer cells choose to use glycolysis even in the presence of abundant oxygen. This phenomenon is termed as the Warburg effect, which is important for cancer cells to meet their energy needs and anabolic requirements. Indeed, several reports indicate that altered expression and activity of key glycoytic enzymes in tumor cells is driven by multiple factors, especially miRNAs (Table 1).

#### Glucose transporters (GLUTs)

Transportation of glucose across the plasma membrane of cancer cells is the first rate-limiting step for glucose metabolism and is mediated by facilitative glucose

**Table 1. Summary of Enzymes Involved in Warburg Effect by miRNAs**

Gene	Upregulated	Downregulated	Reference
<i>Glucose transporters (GLUTs)</i>			
GLUT1	miR-19a, miR-19b, miR-130b, miR-301a	miR 138, miR 150, miR 199a-5p, miR 532-5p, miR 1291	[Yamasaki et al, Chow et al]
GLUT3	Unknown	miR 195-5p	[Fei et al]
GLUT4	miR-223	miR 93, miR-133, miR-150	[Lu et al , Chen et al, Srivastava et al ]
<i>Glycolytic enzymes</i>			
HK2	miR-155	miR 143	[Fang et al , Jiang et al]
GPI	Unknown	miR 200s(miR 200 a/b/c), miR 302b, miR 17-5p	[Ahmad et al , Rengaraj et al]
AldoA	Unknown	miR-122, miR-15a/16-1	[Shea et al, Calin et al]
GAPDH	Unknown	miR-644a	[Sikand et al]
TPI1	Unknown	miR-195, miR-15a/16-1	[Shea et al, Calin et al]
PKM2	miR-99a	miR 133a/b, miR-326, miR-124, miR 137, miR-122, miR-340	[Wong et al , Kefas et al, Li, et al , Sun et al ]
<i>Lactate</i>			
LDHB	Unknown	miR-375	[Kinoshita et al]
MCT1	Unknown	miR-29a/b, miR-124	[Pullen et al ]
Insulin	Unknown	miR-103,miR-107, miR-375, miR-29b	[Trajkovski et al, Zhao et al ,zhou et al]

transporters (Macheda et al., 2005). miRNAs could regulate glucose uptake through mediating the GLUTs expression. miR-1291 has identified as a regulator of GLUT 1 in renal cell carcinoma (Yamasaki et al., 2013). Research in renal cell carcinoma showed that miR 138, miR 150, miR 199a-3p and miR 532-5p downregulate GLUT 1 expression, whereas miR 19a, miR-19b, miR 130b and miR 301a increase GLUT 1 expression (Chow et al., 2010). miR-195-5p suppresses glucose uptake and proliferation through suppression of GLUT3 expression in bladder cancer (Fei et al., 2012). It was confirmed that miR-133 reduced the level of GLUT4 (Horie et al., 2009). miR-223 have been reported that enhanced GLUT4 expression in cardiomyocyte glucose metabolism (Lu et al., 2010). The overexpression of miR-93 resulted in suppression of GLUT4 gene expression in polycystic ovary syndrome patients and women with insulin resistance (Chen et al., 2013). miR-150 has also been reported as a negative regulator of GLUT4 in pancreatic cancer cells (Srivastava et al., 2011).

#### Glycolytic enzymes

Studies showed that miRNAs regulate key enzymes of glycolysis in response to tumor needs. Hexokinases (HKs), four major isoforms: HK1-HK4, HK2 predominant overexpressed in cancer cells. miR-143, a negative regulator of HK2 (Fang et al., 2012; Jiang et al., 2012), miR-155 could indirectly promote HK2 transcription by repressing miR-143 in breast cancer cells (Jiang et al., 2012). Reports demonstrated that miR-200s is associated with regulation of GPI (Ahmad et al., 2011). In addition, GPI expression downregulated by miR-302b and miR-17-5p in chicken primordial germ cells (Rengaraj et al., 2013). miR-122 decreases AldoA expression level in human liver cells (Shea et al., 2010). Additionally, miR-15a/16-1 cluster could inhibit AldoA and TPI1 (Calin et al., 2008). TPI1 also regulated by miR-195, which is significantly down-regulated in the bladder cancer (Ichimi et al., 2009). GAPDH has been used extensively for normalization of gene expression data. Recently, the report showed that

**Table 2. Summary of Enzymes Involved in Mitochondria by miRNAs**

Gene/Function	Upregulated	Downregulated	Reference
<i>TCA cycle</i>			
Acetyl-CoA	miR-103, miR-107	Unknown	[Wilfred et al]
IDH2	Unknown	miR-183	[Tanaka et al, Vohwinkel et al]
SDH	Unknown	miR-210	[Shi et al]
ISCU1/2	Unknown	miR-210	[Shi et al]
MDH	Unknown	miR-743a	[Shi et al]
OXPPOS			
COXIV	miR-181c	miR-181c, miR-338	[Li et al, Das et al]
ROS	miR-128a, miR-210, miR-21, miR-34a, miR-193a-3p	miR-17-92, miR-141, miR-200a	[Ebi et al, Venkataraman et al, Mateescu et al, Zhang et al, Li et al]
GLS	Unknown	miR-23a/b	[Gao et al]
<i>mitochondrial dynamics</i>			
Fis1	Unknown	miR-384	[Wang et al]
Drp-1	Unknown	miR-30, miR-499	[Li et al, Wang et al]

GAPDH are down-regulated by miR-644a. Nevertheless, this miRNA has not yet been described in relation to cancer (Sikand et al., 2012). PKM2 emerges as an important regulator in glycolytic process during cancer development (Sun et al., 2011). PKM2 is regulated by miRNAs, miR-326, miR-133a and miR-133b significantly reduced in tumor cells by mediating PKM2 expression level (Wong et al., 2008; Kefas et al., 2010). Besides, miR-99a directly targets mTOR, then in turn increase PKM2 expression (Li et al., 2013). miR-124, miR-137 and miR-340 inhibits the growth of colorectal cancer cells by counteracting the Warburg effect due to regulating alternative splicing of PKM gene from PKM2 to PKM1 (Sun et al., 2012).

#### *Lactate*

In the glycolytic process, most of the pyruvate is reduced to lactate in cancer cells. The lactate secreted outside the cells by monocarboxylate transports (MCTs) and converted into glucose to recycle back to the tumors. There is no major cancer-associated miRNAs are known to regulate the enzyme LDHA. However, three miRNAs, miR-29a, miR-29b and miR-124, selectively target MCT1 (Pullen et al., 2011). The expression of miR-375 is significantly reduced in cancer tissues of maxillary sinus squamous cell carcinoma (Kinoshita et al., 2012).

#### *Insulin*

Insulin acts in concerting with glucagon in regulation of glucose homeostasis. A growing experimental data shown that miRNAs involved in regulating the secretion and sensitivity of insulin. Silencing of miR-103 and miR-107 have been identified that leads to improved glucose homeostasis and insulin selectivity (Trajkovski et al., 2011). miR-375 overexpression results in reduced glucose-induced insulin secretion and its inhibition enhances insulin secretion (Zhao et al., 2010). The overexpression of miR 29a inhibits cellular proliferation and invasiveness by directly targeting glutamine synthetase in pancreatic cancer cell lines (Zhou et al., 2010).

### **Regulation of mitochondria metabolism by microRNAs**

Mitochondria, are essential to the cell homeostasis maintenance. They play critical roles in regulation of cell events including proliferation, apoptosis, and generation of reactive oxygen species (ROS) (Bienertova-Vasku et al., 2013). Reprogramming of the energy metabolism in cancer cells, is associated mainly with the mitochondria. miRNAs have been reported to be participated in the regulation of mitochondrial function (Table 2), such as TCA cycle, production of ROS, glutamine metabolism and so on (Latronico et al., 2012; Bienertova-Vasku et al., 2013; Tomasetti et al., 2014).

#### *TCA cycle*

Cancer cells, rely more on aerobic glycolysis and less on TCA cycle. Moreover, this metabolic alteration ensures cells to generate multiple biosynthesis materials, while still providing abundant ATP. There is increasing evidence that miRNAs serve as regulators in controlling

TCA cycle. The first definite evidence that miR-103 and miR-107 participate in cellular acetyl-CoA and lipid synthesis through upregulating pantothenate kinase enzyme (Wilfred et al., 2007). mRNA and protein expression levels of IDH2 are downregulated by miR-183 in glioma cells (Vohwinkel et al., 2011; Tanaka et al., 2013). SDH was validated as a bona fide miR-210 target. Recent evidence suggests that oxidative stress can elevate the activity of MDH through reduction of miR-743a in a mouse hippocampal neuronal cell line (Shi et al., 2011). In addition, miR-378(\*) leading to a reduction in TCA cycle gene expression and oxygen consumption (Eichner et al., 2010).

#### *OXPHOS*

Although our understanding of the role of miRNAs on regulation of OXPHOS is still far from complete, these are some studies have confirmed that some microRNAs participate in regulation of the ETC-related protein level. Overexpression of miR-338 results in a low COX IV mRNA as well as protein levels and can significantly reduce mitochondrial oxygen consumption, ATP production (Li et al., 2012). Overexpression of miR-181c results in down-regulation of COX1 protein and increased COX2 mRNA and protein levels, with an increase in both mitochondrial respiration and ROS generation in neonatal rat ventricular myocytes (Das et al., 2012).

#### *ROS*

Emerging research shown that ROS level mediated by microRNAs. The first evidence for the role of miRNAs on ROS production, miR-17-92 overexpression may serve as a fine-tuning influence to counterbalance the generation of DNA damage in RB-inactivated lung cancer cells (Ebi et al., 2009). miR-128a, increases intracellular ROS level and further impairs growth activity of medulloblastoma cells (Venkataraman et al., 2010). miR-141 and miR-200a, two members of the miR-200 family, act on ovarian tumorigenesis by targeting p38 $\alpha$  and modulate the oxidative stress response (Mateescu et al., 2011). In addition, miR-21 and miR-34a promotes tumor malignant growth and progression through its upregulation of cellular ROS levels (Zhang et al., 2012; Li et al., 2014).

#### *Glutamine metabolism*

Glutamine, is a major source of energy and nitrogen for biosynthetic pathways, and a carbon substrate for anabolic processes in cancer cells. Glutaminase is critical for mitochondrial metabolism, it converts glutamine to glutamate and ammonia. Myc as a transcriptional regulator, is necessary for cells to engage in glutaminolysis, which exceeds the cell requirement for nucleic acid and protein synthesis. A consequence of this Myc-dependent glutaminolysis is the alteration from mitochondrial metabolism to depend on glutamine catabolism to maintain cell viability and TCA cycle anapleurosis (Wise et al., 2008). Recent studies uncovered that miR-23a and miR-23b are suppressed by Myc, whereas, miR-23a/b is known to target and repress expression of glutaminase in human lymphoma and prostate cancer cells (Gao et al., 2009).

*Mitochondrial dynamics*

Mitochondria are dynamic organelles, two necessary processes of fusion and fission are vital to the maintenance of organelle fidelity. Mitochondria fission is involved in the initiation of apoptosis, the aberrant mitochondrial fission participates in the pathogenesis of many diseases including cancer. Studies have reported that miRNAs are able to regulate mitochondria fission machinery. miR-384 is able to suppress mitochondria fission by targeting Fis1, which is necessary for mitochondrial fission and apoptosis (Wang et al., 2012). miR-30 family members inhibited mitochondrial fission through suppressing the expression of p53 and its downstream target dynamin-related protein-1 (Drp1) (Li et al., 2010). Additionally, miR-499 can inhibit cardiomyocyte apoptosis through its suppression of calcineurin-mediated dephosphorylation of Drp-1 (Wang et al., 2011).

In conclusion, cancer metabolism and the role of miRNAs are rapidly growing research area. miRNAs participate in controlling cancer cell metabolic reprogramming, including glycolysis and mitochondrial energy metabolism. miRNAs play important roles by regulating the expression of gene that modulating the various metabolic phenotypes or metabolic-related enzymes. Although Warburg was wrong about mitochondria, he was prescient in his focus on metabolism. Mitochondria represent an essential center of physiological processes of the cell, whose deregulation largely contributes to the cancer initiation and progression. Recently, many studies showed miRNAs as modulators of mitochondrial processes, including Warburg effect, which reinforce their importance in tumor biology, and highlight these gene regulators as promising therapeutic targets in cancers. Altered metabolism should now be considered a core hallmark of cancer. There is much work to be done.

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