

# Regulation of Glycolysis by Non-coding RNAs in Cancer: Switching on the Warburg Effect

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**The “Warburg effect” describes the reprogramming of glucose metabolism away from oxidative phosphorylation toward aerobic glycolysis, and it is one of the hallmarks of cancer cells. Several factors can be involved in this process, but in this review, the roles of non-coding RNAs (ncRNAs) are highlighted in several types of human cancer. ncRNAs, including microRNAs, long non-coding RNAs, and circular RNAs, can all affect metabolic enzymes and transcription factors to promote glycolysis and modulate glucose metabolism to enhance the progression of tumors. In particular, the 5′-AMP-activated protein kinase (AMPK) and the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathways are associated with alterations in ncRNAs. A better understanding of the roles of ncRNAs in the Warburg effect could ultimately lead to new therapeutic approaches for suppressing cancer.**

Otto Heinrich Warburg first discovered that tumors tended to show a specific metabolic phenotype in the 1920s. Cancer cells, even when they have sufficient oxygen, tend to make ATP using glycolysis, rather than the oxidative phosphorylation (OXPHOS) that occurs in normal cells and generates more ATP per glucose molecule. This phenomenon of aerobic glycolysis became known as the “Warburg effect.” In glycolysis, the glucose uptake by the cancer cells is higher, and lactic acid is produced from pyruvate, thus reducing the pH of the tumor.<sup>1,2</sup> Soon after the discovery, Warburg proposed that the mitochondrial function was fundamentally altered in tumor cells, and he even proposed that this could be a cause of cancer.<sup>3</sup> However, he subsequently stated that mitochondrial function was not damaged in most kinds of cancer cells.<sup>4</sup>

Moreover, Warburg suggested that the increase in glucose/glutamine consumption by cancer cells could lead to them becoming “glucose addicted” or “glutamine addicted,” which may induce cell death. Metabolic intermediates that are produced by cells through glucose/glutamine catabolism act as building blocks and reducing agents for the production of macromolecules and the generation of ATP.<sup>5</sup>

In addition to ATP, rapidly proliferating cancer cells have a high requirement for proteins, membrane phospholipids, nucleic acids, and fatty acids. Glycolysis can provide intermediates and substrates for producing many biological macromolecules. It also produces small molecules or precursors, such as non-essential amino acids, acetyl-coenzyme A (CoA), and ribose for the biosynthesis of nucleo-

tides needed for the rapid replication of DNA.<sup>3,4,6</sup> The increased metabolism of tumors tends to create high quantities of reactive oxygen species (ROS). In tumor cells, these ROS can trigger senescence and apoptosis caused by oxidative stress.<sup>7</sup>

The “reverse Warburg effect” defines a situation when cancer-associated stromal cells could metabolically support adjacent cancer cells by carrying out glycolysis. The transfer of metabolites can induce stromal cell-cancer cell coupling, which could allow cancer cells to generate more ATP in order to support proliferation.<sup>8</sup>

The switch to glycolysis away from OXPHOS therefore tends to reduce the levels of ROS generated in the mitochondria. The glycolytic intermediates provide the required sources of carbon for rapid cell proliferation, but less ATP is formed compared to OXPHOS.<sup>9</sup> The lactate produced by glycolysis reduces the pH levels in the extracellular matrix (ECM).<sup>10</sup> The acidic microenvironment can enhance tumor invasion and metastasis, while also increasing the resistance to treatment with ionizing radiation.<sup>11,12</sup> Therefore, the Warburg effect can be regarded as a pathway in which tumor cells harness cellular stress to progress.<sup>13,14</sup> In the Warburg effect, it is proposed that the cellular metabolism is adapted to increase the incorporation of molecules into the biomass, such as nucleotides, amino acids, and lipids, which are needed for production of new cells. In support of this idea, numerous signaling pathways involved in cell proliferation can also regulate the metabolic pathways that incorporate nutrients into the biomass. Moreover, specific cancer-associated mutations could enable cancer cells to take up and metabolize nutrients in a way that is conducive to proliferation rather than ATP production.<sup>3</sup>

Additionally, it has been found that glycolysis in cancer cells is regulated by N<sup>6</sup>-methyladenosine modifications in several mRNAs. Pyruvate dehydrogenase kinase 4 is involved in N<sup>6</sup>-methyladenosine-regulated glycolysis. When the 5′ untranslated region (UTR) of pyruvate dehydrogenase kinase 4 is modified with N<sup>6</sup>-methyladenosine, translation elongation is improved by binding to the YTHDF1/eEF-2

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complex. Moreover, mRNA stability can also be improved by interacting with IGF2BP3.<sup>15</sup> Although most  $N^6$ -methyladenosine modifications take place on mRNAs, it has been shown that  $N^6$ -methyladenosine modifications can also occur with noncoding RNAs, especially miRNAs and circular RNAs (circRNAs).<sup>16</sup>

Many proteomic and genomic pathways are involved in the initiation and progression of cancer.<sup>17–19</sup> Genome-wide surveys of cancer cells have revealed that there are frequent changes or variations in copy number located within non-coding regions of the DNA.<sup>17,20</sup> In the human genome, it has been reported that 95% of the total sequence do not actually code for proteins. This non-coding DNA (ncRNA) is transcribed to produce tens of thousands of functional ncRNAs. These ncRNAs include small interfering RNAs (siRNAs), microRNAs (miRNAs), long ncRNAs (lncRNAs), and antisense RNAs (asRNAs).<sup>20–23</sup> Recently, new types of ncRNAs, namely circRNAs, have been reported.<sup>24–26</sup> A large portion of the circRNAs are produced from the exons of coding genes, but many of them do not encode any protein.<sup>24–26</sup>

### Glycolysis in Cancer

As reviewed by Zhang and Yang,<sup>27</sup> cancer cells frequently tend to display the glycolytic phenotype. Bonnet et al.<sup>28</sup> suggested that by switching the glycolytic phenotype toward OXPHOS, this could cause the cancer cells to die. In addition, the restoration of the mitochondrial- $K^+$  channel function was enough to enhance apoptosis because the mitochondrial- $K^+$  channel axis of cancer cells was suppressed. This study provided two important hypotheses: (1) glycolysis facilitates the growth of tumor notwithstanding a suppressed mitochondrial- $K^+$  channel axis, and (2) reversal of the glycolytic phenotype back to OXPHOS may enhance cancer cell death.

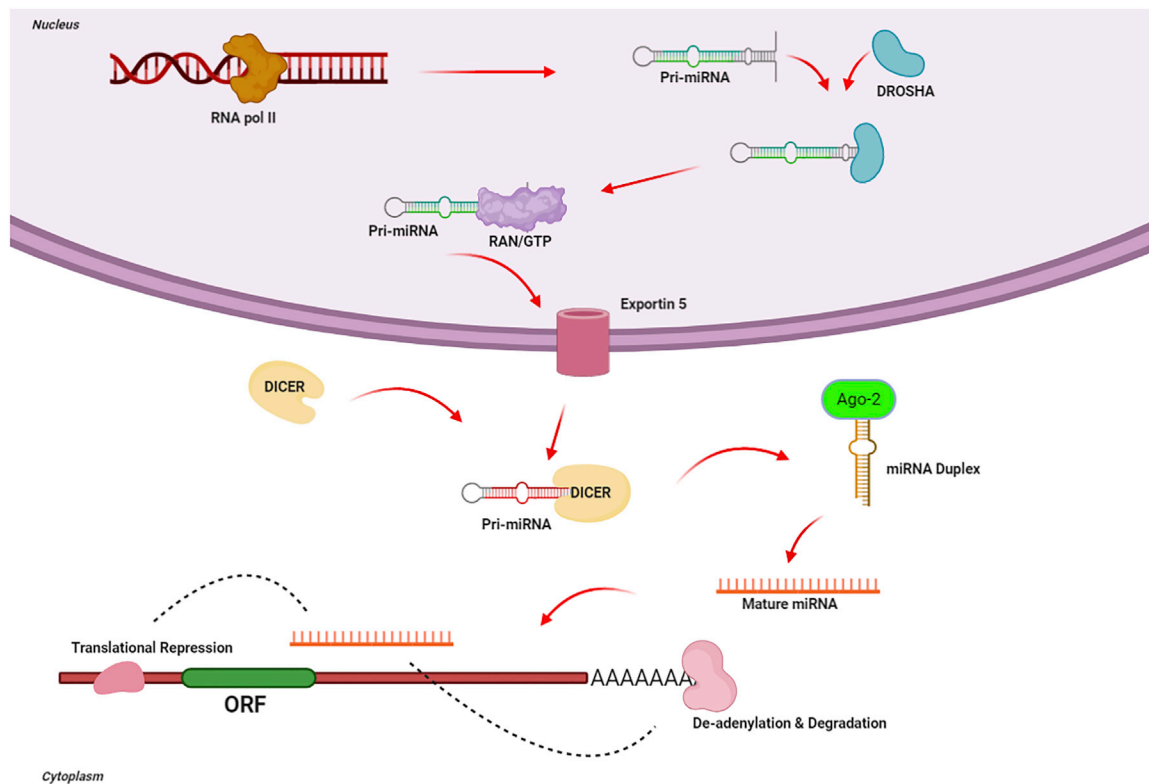
The lack of a sufficient blood supply, which is characteristic of rapidly growing tumors, causes areas of hypoxia in which OXPHOS is inactive, and a metabolic switch from mitochondrial respiration to glycolysis is accompanied by mitochondrial dysfunction.<sup>29,30</sup> In functionally active mitochondria, the occurrence of aerobic glycolysis under normoxic conditions is intriguing. It is noteworthy that mutations in mitochondrial DNA (mtDNA) can affect the enzymes of OXPHOS, in particular three enzymes, that is, isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate dehydrogenase (FDH) (reviewed by Wallace<sup>31</sup>). Similarly, mutations in the nuclear DNA (nDNA) can also affect the bioenergetics of cancer cells.<sup>31</sup> These changes in enzyme activity are related to many cellular pathways, and the metabolic machinery of cancer cells can be reprogrammed; for example, SDH mutations lead to the accumulation of succinate, which inhibits prolyl hydroxylase dehydrogenase (PHD) and finally causes hypoxia-inducible factor (HIF)-1 $\alpha$  stabilization. This mechanism links HIF-1 $\alpha$  and angiogenesis to aerobic glycolysis and lactate production.

However, the laboratory depletion of mtDNA in cancer cells using ethidium bromide (rho zero cells) led to a decreased growth rate and colony formation and inhibited tumorigenicity.<sup>32</sup> These rho

zero cells showed an increased sensitivity to cytotoxic drugs, thus refuting the argument that drug resistance was based on functional mitochondria. Warburg's original statement that dysfunctional mitochondria were a "common cause of cancer growth" must now be seen to be more complex. Transfer of mitochondria from adjoining normal healthy cells can compensate for the function of OXPHOS.<sup>33</sup> However, although the exact relationship between alterations of mitochondrial function and the cancer phenotype remains controversial, the energy metabolism of cancer cells, in particular glycolysis and lactate production, is considered a valid target for therapeutic intervention.

Despite the fact that glycolysis produces a lower amount of ATP compared to mitochondrial OXPHOS, tumors can still derive some benefits from the switch.<sup>34</sup> First, the rate of turnover in the glycolytic enzymes is much higher (up to 100 times faster) compared to OXPHOS.<sup>35</sup> The low yield of ATP but the high rate of production<sup>36</sup> means that there are selective benefits in the case of shared energy sources, proposing an evolutionary advantage to glycolysis.<sup>37</sup> Rapidly dividing cells such as microorganisms with a doubling time in the range of a few minutes to several hours require ATP for proliferation, while cancer cells with a relatively longer doubling time (~24 h) require ATP more for cell maintenance, although their proliferation is still rapid compared to normal cells. Hence, for the growth of cancer, the ATP made by glycolysis is sufficient, but the rapid rate provides a selective growth benefit.<sup>38,39</sup> In addition to ATP, cancer cells need a more abundant supply of metabolic precursors and intermediates, which are essential for the biosynthesis of macromolecules and for increasing the tumor mass.<sup>40</sup> The accumulation of glycolytic intermediates has been found to be important for the pentose phosphate pathway (PPP), leading to the generation of ribulose-5-phosphate and NADPH. Both molecules are necessary for the biosynthesis of nucleic acids and lipids. Finally, the increased NADPH levels allows the cancer cells to maintain adequate levels of reduced glutathione (GSH), which is an important non-enzymatic antioxidant. GSH plays a fundamental role in the protection of cancer cells from their elevated levels of ROS, and from damage caused by anti-neoplastic agents and chemotherapeutic drugs.<sup>41,42</sup> In this regard, Zhou et al.<sup>37</sup> showed that chemoresistant cell lines had elevated levels of aerobic glycolysis, demonstrating a biochemical connection between glycolysis and chemoresistance. Additionally, aerobic glycolysis has been implicated in the resistance of cancer cells to radiotherapy.<sup>43</sup>

KRAS can act as an oncogene by altering the metabolism of cancer cells in many ways, such as increasing the uptake of glucose, and triggering glycolysis even in the presence of oxygen (the Warburg effect).<sup>44</sup> These effects of oncogenic KRAS are due to the upregulation of the expression of glucose transporters as well as glycolytic enzymes.<sup>45</sup> Amendola et al.<sup>46</sup> found that hexokinase 1 (HK1) can interact with KRAS4A, which can change the activity of the kinase, and suggested that HK1 could be considered as an effector of KRAS4A. The palmitoylation-depalmitoylation cycle that KRAS4A undergoes enables co-localization with HK1 at the outer membrane of mitochondria. Therefore, KRAS4A expression in different cancer



**Figure 1. Mechanism of miRNA Biogenesis**

miRNAs are initially transcribed as a long 5'-capped and 3'-polyadenylated pri-miRNA. The Drosha complex transforms the pri-miRNA into a hairpin-shaped pre-miRNA. Exportin-5 exports the pre-miRNA into the cytoplasm, where it is further processed by Dicer. The double-stranded miRNA is dissociated, and the mature miRNA strand is combined in the RISC where it carries out gene silencing by increasing the degradation of target mRNAs or by translational inhibition.

cells may drive specific metabolic alterations that could be used as therapeutic targets.

The pyruvate kinase isoform (pyruvate kinase M2 [PKM2]), an alternatively spliced product of the PKM2 gene, can alter glucose metabolism in cancer cells and increase tumorigenesis. This function is due not to its known enzyme activity, but to a direct interaction with the HIF-1 subunit HIF-1 $\alpha$ , leading to the transactivation of HIF-1 target genes through increasing the binding of HIF-1 and recruitment of p300 to the hypoxia response elements.<sup>47</sup>

The PPP plays an important role in the biosynthesis of macromolecules, and recent studies have associated it with antioxidant protection and resistance to radiation and chemotherapy.<sup>48</sup> The transketolase (TKTL1) enzyme is particularly involved in cell survival under starvation and stress conditions.<sup>49–51</sup> Other reports have indicated that TKTL1 can influence the chemosensitivity of cancer cells to cetuximab<sup>52</sup> and imatinib.<sup>53</sup> Therefore, it is clear that aerobic glycolysis together with the pentose shunt pathway can provide multiple advantages to cancer cells, including for tumor progression and development of resistance to treatment. Therefore,

tumor glycolysis could present a promising target for therapeutic intervention.

### miRNA Biogenesis

The biosynthesis mechanism of miRNA is evolutionarily conserved. The pathway involves successive endonuclease cleavage steps mediated by two ribonuclease (RNase) III enzymes called Dicer and Drosha (see Figure 1).<sup>54</sup> The primary miRNA transcript (pri-miRNA) is produced in the nucleus by RNA polymerase II (RNA Pol II). The pri-miRNA is transformed by Drosha into a hairpin structure of ~60–100 nt, called the precursor-miRNA (pre-miRNA) (see Figure 1).<sup>55–58</sup> The pre-miRNA is carried out of the nucleus by the interaction between Ran-GTP and exportin-5. The pre-miRNA then undergoes further processing catalyzed by Dicer (see Figure 1)<sup>59,60</sup> to produce an ~22-nt double-stranded RNA (dsRNA) construct composed of the passenger (miRNA\*) strand and the mature miRNA guide strand (see Figure 1). The mature miRNA strand binds to the 3' UTR of its target genes. This binding triggers the assembly of a large protein complex called the RNA-induced silencing complex (RISC), which reduces gene expression, either by the degradation of the mRNA or by inhibiting translation.<sup>61</sup>

The binding of the miRNA to the miRNA-recognition site in the 3' UTR of the target mRNA can accommodate incomplete base pairing within the sequence. The incomplete nature of the binding between miRNA and mRNA means that any single miRNA could potentially target tens to hundreds of different mRNAs.<sup>62–64</sup> The miRNA-RISC complex increases mRNA degradation and translational inhibition, causing silencing of the particular gene.<sup>65–69</sup> These effects are heavily involved in cell differentiation, embryonic development, cell death, metabolism, and proliferation.<sup>70–72</sup>

### Regulation of Glycolysis by miRNAs in Cancer

Many different oncogenes and tumor suppressor genes are regulated by miRNAs.<sup>73</sup> The effects of miRNAs on gene regulation have been reported in the pathogenesis of cancers originating in multiple origins and composed of different cell types.<sup>74–76</sup>

Among other cellular functions, miRNA can regulate metabolic pathways, many of which are altered in cancer. The changes in tumor metabolism have been associated directly or indirectly with the downstream targets of many different miRNAs.<sup>77</sup> Table 1 lists the glycolytic pathways involved in cancer that have been reported to be regulated by miRNAs, either directly or at the level of oncogenes.

The glucose transporter (GLUT) family of receptors (GLUT1–GLUT4) mediates transport of glucose through the plasma membrane of eukaryotic cells. GLUT3 as well as GLUT1 are mostly unmodified in many cancer types.<sup>157</sup> However, GLUT4 activity is regulated by insulin or insulin-like growth factor (IGF) signaling, whereas the function of GLUT3 and GLUT1 is independent of insulin.<sup>158–160</sup> Many miRNAs have been found to regulate the expression levels of GLUT3 and GLUT1, although none of these has been experimentally shown to target the mRNA levels of GLUT3 or GLUT1. However, the expression of GLUT4 was reduced by miRNA (miR)-133 and miR-223 in cardiomyocytes.<sup>161,162</sup> Whether the expression levels of GLUT4 are involved in the metabolic phenotype in cancer remains to be investigated.

The targets of miRNAs include some glycolytic enzymes. The first step in the glycolytic pathway is the action of hexokinases (HKs) that are responsible for a transferring a phosphoryl group from ATP to the 6-hydroxyl of glucose for synthesizing glucose-6-phosphate (G6P). In this manner, glucose phosphorylation directs the glucose into the cells by maintaining the gradient essential for facilitative GLUTs. There is no evidence yet suggesting the role of miRNAs in regulating HKs.<sup>163</sup> The miR-200 family (miR-200a, miR-200b, and miR-200c) regulates phosphoglucose isomerase that plays roles in the invasion and metastasis of cancer cells.<sup>164</sup> Mimetics of miR-122 acting in human and rat liver cells regulate aldolase A (ALDOA).<sup>165</sup> Phosphoglycerate kinase 1 (PGK1), enolase 1 (ENO1), ENO2, and triosephosphate isomerase 1 (TPI1) are all regulated by the miR-17-92 cluster.<sup>166</sup> However, there are no target sites for miRNAs (miR-17-92) within these genes. The regulation of HIFs by the miR-17-92 cluster affects some glycolytic genes.<sup>166</sup> One of the targets for miR-195 is TPI1, which was found to be downregulated in bladder cancer.<sup>167</sup>

However, a direct relationship has still to be confirmed. TPI1 and ALDOA were detected in a proteomic screen carried out in MEG-01 leukemic cells to be regulated through the miR-15a/16-1 cluster, and they were downregulated or eliminated in chronic lymphocytic leukemia (CLL) B cells.<sup>168</sup> TPI1 was also predicted to be a direct target of the miR-15a/16-1 cluster. ALDH6A1 (aldehyde dehydrogenase 6 family member A1) was detected in a microarray screen in CLL to be regulated by the miR-15a/16-1 cluster.<sup>168</sup> The expression levels of the target genes of phosphoglucose mutase 1 (PGM1), ENO1, and PGK1 were detected using proteomic analysis in the invasive lung cancer cell line DLKP-A and found to be modulated by miR-29a.<sup>169</sup> The mechanism involved miRNA downregulating ENO2d in the HepG2 hepatocarcinoma cell line, and this was confirmed because ENO2 levels were significantly upregulated by Droscha knockdown.<sup>170</sup> Nevertheless, the details of ENO2-targeting miRNAs are so far unclear. Some cancer cells significantly overexpress PKM2, which is a direct target of miR-326.<sup>170</sup> In solid tumors, the gene for PKM2 is also targeted by miR-133a and miR-133b.<sup>171</sup>

A large amount of pyruvate is converted into lactate, instead of acetyl-CoA embracing the mitochondrial Krebs cycle, within the glycolysis in cancer cells. The produced cytosol lactate leaves the cells with the help of monocarboxylate transporters (MCTs). In a study on human pancreatic cancer, the molecular mechanisms of miR-124 to regulate glycolysis were evaluated by Wu et al.,<sup>78</sup> who found higher expression of MCT1 in PDAC tissue when comparing with normal tissue. The metabolism of lactate is influenced by the MCT1 inhibition, and the results are increased intracellular pH and decreased PANC-1 cell proliferation. The target gene of miR-124 is MCT1. The results of an *in vitro* study showed that the glycolytic activity of PANC-1 cells is impeded by miR-124 through targeting MCT1, which causes a decrease in the tumor phenotype by raising the intracellular pH via LDH-A and HIF-1 $\alpha$ . The tumor growth was significantly blocked by miR-124 overexpression and MCT1 silencing within an *in vivo* study. In the lactate metabolic pathway, the PANC-1 progression is inhibited by miR-124 through MCT1 targeting. The results from the present study reported new findings regarding further functional studies of miR-124 that predispose potential therapeutic strategies to PDAC.<sup>78</sup>

According to Pullen et al.,<sup>172</sup> DNA methylation at the Mct1 promoter is probably associated with cell type-specific transcriptional repression (three miRNAs, i.e., miR-29a, miR-29b, and miR-124) selectively targeting MCT1 3' UTRs in humans and mice. The effects of the miRNAs of mutated miR-29 or miR-124 binding sites are blocked, meaning a direct function of these miRNAs on the MCT1 message. Although it is expressed in the mouse  $\beta$  cell line MIN6, no expression of miR-124 was evident in mature mouse islets, whereas the three miR-29 isoforms are expressed and enriched in mouse islets in large amounts. According to our results, Mct1 mRNA levels are elevated due to miR-29a inhibition in primary mouse islets, so that the isoforms of miR-29 cause  $\beta$  cell-specific silencing of the MCT1 transporter and influence the secretion of insulin.<sup>172</sup>

**Table 1. Selected MicroRNAs Involved in the Regulation of Glycolysis Processes in Various Cancers**

Cancer	MicroRNAs	Expression in Cancer	Target	Model	Samples	References
Pancreatic cancer	miR-124	downregulation	MCT1, PANC-1	<i>in vitro</i>		78
	miR-7	downregulation	LKB1-AMPK-mTOR	<i>in vitro</i>		79
	miR-135	upregulation	phosphofructokinase-1	<i>in vitro, in vivo</i>		80
Glioma	miR-218	upregulation	HK2, Bim1	<i>in vitro, human</i>	21	81
	miR-150	upregulation	HIF-1 $\alpha$	<i>in vitro</i>		82
	miR-451	downregulation	GLUT1	<i>in vitro</i>		83
	miR-200b	downregulation	LDHA	<i>in vitro</i>		84
Hepatocellular carcinoma	miR-491-5p	downregulation	PKM2	<i>in vitro</i>		85
	miR-142-3p	downregulation	LDHA	<i>in vitro</i>		86
	miR-125b	downregulation	HK2	<i>in vitro, in vivo</i>		87
	miR-125a	downregulation	HK2	<i>in vitro, in vivo</i>		88
	miR-199a-5p	downregulation	HIF-1 $\alpha$	<i>in vitro</i>		89
	miR-505	downregulation	IGF-1R	<i>in vitro, human</i>	60	90
Liver cancer	miR-34a	downregulation	LDHA	<i>in vitro, human</i>	22	91
	miR-139-5p	downregulation	HK1, PFKFB3	<i>in vitro, in vivo</i>		92
Gastric cancer	miR-21-5p	upregulation	PDHA1	human	46	93
	miR-34a	downregulation	LDHA	human	73	94
	miR-214	upregulation	A2AR, PRDM16	<i>in vitro</i>		95
	miR-139-5p	downregulation	PRKAA1	<i>in vitro</i>		96
	miR-148b	downregulation	GLUT1	<i>in vitro</i>		97
	miR-181b	downregulation	HK2	<i>in vitro</i>		98
Renal cell carcinoma	miR-409-3p	downregulation	PDK1	<i>in vitro</i>		99
	miR-143	downregulation	K-RAS	<i>in vitro, in vivo, human</i>		100
	miR-15b-5p	downregulation		<i>in vitro</i>		101
Osteosarcoma	miR-323a-3p	downregulation	LDHA	<i>in vitro</i>		102
	miR-33b	downregulation	LDHA	<i>in vitro</i>		103
	miR-125b	downregulation	HK2	<i>in vitro</i>		104
	miR-186	downregulation	PTTG1 and HIF-1	<i>in vitro</i>		105
	miR-150	downregulation	Glut1	<i>in vitro</i>		106
	miR-185	downregulation	hexokinase 2	<i>in vitro, human</i>	30	107
Testicular tumors	miR-199a-3p	downregulation	LDHA, Sp1	<i>in vitro</i>		108
Tongue squamous cell carcinoma	mitomiR-2392	upregulation	HK2 and PKM2	<i>in vitro, in vivo</i>		109
Breast cancer	miR-27b	upregulation	PDHX	<i>in vitro</i>		110
	miR-31	downregulation	DNMT3	<i>in vitro</i>		111
	miR-155	upregulation	PIK3R1-PDK/AKT-FOXO3a-cMYC	<i>in vitro</i>		112
	miR-340	downregulation	MCU	<i>in vitro</i>		113
	miR-30a-5p	downregulation	LDHA	<i>in vitro</i>		114
	miR-342-3p	downregulation	MCT1	<i>in vitro, in vivo, human</i>	146	115
Lung cancer	miR-31-5p	upregulation	HIF-1 $\alpha$ inhibitor	<i>in vitro, in vivo</i>		116
	miR-214	upregulation	HK2, PKM2, PTEN/Akt/mTOR	<i>in vitro</i>		117
	miR-449a	downregulation	LDHA	<i>in vitro</i>		118

(Continued on next page)



Table 1. Continued

Cancer	MicroRNAs	Expression in Cancer	Target	Model	Samples	References
Cancer	miR-124	downregulation	AKT-GLUT1/HK2	<i>in vitro</i>		119
	miR-155	upregulation	HK2	<i>in vitro</i>		120
	miR-144	downregulation	GLUT1	<i>in vitro</i>		121
Ovarian cancer	miR-14	upregulation	HK2, DNMT3A	<i>in vitro</i>		122
	miR-603	downregulation	HK2	human	21	123
	miR-21	upregulation	HK2, PKM2, and LDHA	<i>in vitro</i>		124
	miR-383	downregulation	LDHA	<i>in vitro</i>		125
	miR-203	upregulation	PDHB	<i>in vitro, in vivo</i>		126
	miR-450a	downregulation	TIMMDC1, MT-ND2, ACO2, ATP5B	<i>in vitro, in vivo</i>		127
	miR-603	upregulation	HK2	<i>in vitro, in vivo, human</i>	21	123
Gall bladder carcinoma	miRNA-139-5p	downregulation	PKM2	<i>in vitro, in vivo</i>		128
	let-7a-5p	upregulation	PKM2, Stat3	<i>in vitro</i>		129
	miR-30d-5p	downregulation	LDHA	human		130
Laryngeal squamous cell carcinoma	miR-125b-5p	downregulation	HK2	<i>in vitro, human</i>		131
Prostate cancer	miR-29c	downregulation	SLC2A3	<i>in vitro, human</i>	57	132
	miR-137	upregulation	NOX4	<i>in vitro</i>		133
	miR-101	downregulation	NADPH, TIGAR	<i>in vitro</i>		134
	miR-132	downregulation	GLUT1	<i>in vitro</i>		135
Bladder cancer	miR-200c	downregulation	LDHA	<i>in vitro</i>		136
	miR-361-5p	downregulation	Sp1/PKM2	<i>in vitro</i>		137
	miR-145	downregulation	KLF4/PTBP1/PKM2s	<i>in vitro</i>		138
	miR-204-3p	downregulation	LDHA	<i>in vitro, human</i>	60	139
Melanoma	miR-625-5p	downregulation	PKM2	<i>in vitro</i>		140
	miR-137	downregulation	GLO1	<i>in vitro</i>		141
	miR-33a-5p	downregulation	HIF-1 $\alpha$	<i>in vitro, human</i>	20	142
	miR-33b	downregulation	HIF-1 $\alpha$	<i>in vitro</i>		143
	miR-370	upregulation	PDHB	human	41	144
Colorectal cancer	miR-23a~27a~24 cluster	upregulation	HIF-1 $\alpha$	<i>in vitro</i>		145
	miR-9-5p, miR-98-5p, and miR-199-5p	upregulation	HK2	human	40	146
	miR-142-5p	upregulation	SDHB	<i>in vitro</i>		147
	miR-328	downregulation	SLC2A1/GLUT1	human	47	148
	miR-1	downregulation	HIF-1 $\alpha$ , HK2, MCT4	<i>in vitro, in vivo</i>		149
	miR-98	upregulation	HK2	<i>in vitro, human</i>	215	150
Esophageal squamous cell carcinoma	miR-143	downregulation	HK2	<i>in vitro, human</i>	8	151
Nasopharyngeal carcinoma	miR-34b-3, miR-449a	downregulation	LDHA	<i>in vitro</i>		152
Cutaneous squamous cell carcinoma	miR-365	upregulation	HK2, GLUT1, PDK1	<i>in vitro</i>		153
Oral squamous cell carcinoma	miR-143	downregulation	HK2	<i>in vitro</i>		154
Thyroid cancer	miR-125a-5p	downregulation	CD147	<i>in vitro</i>		155
	miR-143	downregulation	HK2	<i>in vitro, in vivo</i>		156

Aberrant miR-1 expression in aerobic glycolysis (the Warburg effect) was shown by Xu et al.<sup>149</sup> in cancer cells. The aerobic glycolysis and proliferation of tumor cells were blocked by miR-1 because of Smad3 inactivation and HIF-1 $\alpha$  targeting. Therefore, the expression of HK2 and MCT4 was decreased, indicating a new pathway that mediates aerobic glycolysis in cancer cells. The tumor glycolysis was reduced significantly following the overexpression miR-1 mimics, including the generation of lactate and the absorption of glucose, as well as cell proliferation, and ectopic Smad3 expression reversed these effects. HIF-1 $\alpha$  is regulated by and interacts with endogenous Smad3; this activates Smad3, which is significantly suppressed by miR-1 addition. Based on their results, Smad3 has a pivotal role in the effects of miR-1 in colorectal cancer cells. This presents a mechanism for the first time so that the Warburg effect is provided easily by the miR-1/Smad3/HIF-1 $\alpha$  axis in enhancing cancer progression, *in vitro* and *in vivo*. miR-1 is associated with tumor suppression, and thus it can act as a suppressor in molecular therapy of patients suffering from advanced colorectal cancer.<sup>149</sup>

The tumor cells frequently overexpress lactate dehydrogenase A (LDHA). Wang et al. observed higher LDHA levels in patients with colorectal cancer when comparing samples with adjacent normal tissue.<sup>173</sup> The production of lactate and ATP and the adsorption of glucose were reduced following LDHA knockdown. A much slower growth rate was seen for the colorectal cancer cells with LDHA knockdown compared to the control cells. Their results showed that LDHA is targeted by miR-34a, miR-34c, miR-369-3p, miR-374a, and miR-4524a/b, thereby regulating glycolysis in cancer cells. In colorectal cancer tissues, an inverse correlation has been found between these miRNAs and LDHA expression. They detected a genetic loci related to the high progression of colorectal cancer, that is, rs18407893 at 11p15.4 (in the 3' UTR of LDHA), which maps to the seed sequence identified by miR-374a. The LDHA level is lower in cancer cells overexpressing miR-374a than in miR-374a-mutant (MUT) (rs18407893 at 11p15.4). These new results can present promising therapeutic strategies to the Warburg effect and therapeutic targets of cancer energy metabolism.<sup>173</sup>

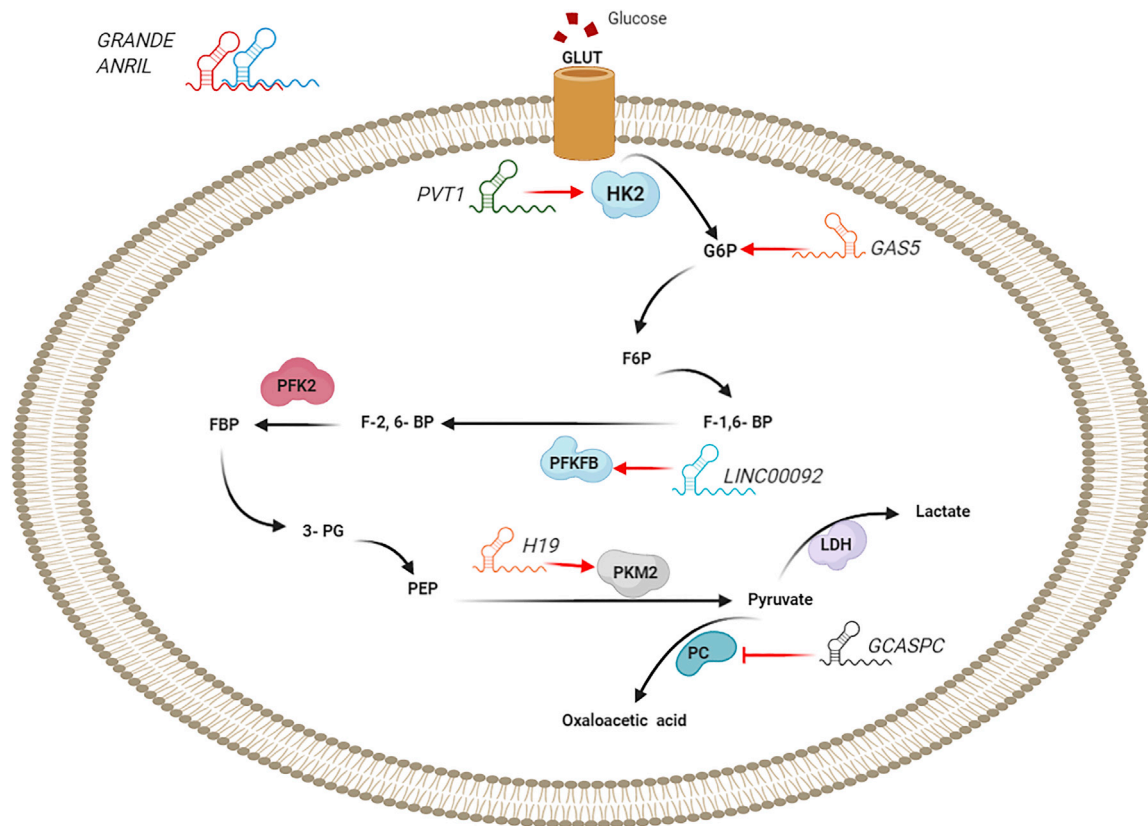
Yuan et al.<sup>136</sup> in their studies evaluated the expression and function of LDHA in bladder cancer and reported the upregulation of LDHA in bladder cancer cells, enhancing proliferation, invasion, and glycolysis. According to their results, LDHA is targeted directly by miR-200c in bladder cancer cells. As well, LDHA-induced glycolysis, cell proliferation, and invasion were inhibited by ectopic expression of miR-200c. In fact, one of the possible therapeutic approaches can be LDHA targeting via miR-200c in bladder cancer. Mammalian cells extracted an array of cellular processes for maintaining their survival by improving glycolysis and considering low oxygen hypoxia or tension. Under these conditions, the use of genes was operated frequently by HIF-1 $\alpha$ , which is fundamental for the helix-loop-helix transcription element of the PAS family.<sup>174</sup> The factor of transcription act as a function of a heterodimer of HIF-1 $\beta$  and HIF-1 $\alpha$ . Note that HIF-1 $\alpha$  protein can be degraded due to existing oxygen (normoxia) by the ubiquitin-proteasomal proced-

ure, whereas HIF-1 $\beta$  and HIF-1 $\alpha$  are basically transcribed and translated.

Kelly et al.<sup>175</sup> specified enzyme glycerol-3-phosphate dehydrogenase 1-like (GPD1L) as a new regulator of a direct target of miR-210 and HIF-1 $\alpha$  stability. In response to the expression of miR-210, the levels of HIF-1 $\alpha$  were stabilized by reduced levels of GPD1L, leading to enhancing HIF-1 $\alpha$  target genes. The enhancement of HIF-1 $\alpha$  protein levels and hypoxia-induced miR-210 suppresses GPD1L by suppression of PHD activity. Different influences of HIF-1 $\alpha$  onto the transcription of metabolic genes were determined to be straight; nevertheless, HIF-1 $\alpha$  additionally adjusts a number of miRNAs, including miR-210, that can regulate an excess of genes in various physiological functions. In multiple cancers, miR-210 can be overexpressed dramatically.<sup>176–179</sup> In addition, it suppresses ISCU1/2 and hence reduces the activity of prototypical iron-sulfur proteins controlling mitochondrial metabolism, consisting of complex I as well as aconitase, by taking into account hypoxic conditions.<sup>180</sup> However, miR-210 suppresses mitochondrial respiration and can be a reason for more aerobic glycolysis in cancer, indirectly. By apparatuses independent of aerobic glycolysis, many miRNAs may overall affect the homeostasis of glucose. miR-375, known as one such miRNA, can adjust glucose homeostasis in the body with the modulation of insulin secretion. In  $\beta$  cells, the mentioned overexpression prevents insulin exocytosis with related mechanisms, which are independent of variations in the intracellular Ca<sup>2+</sup> signaling and transmembrane Ca<sup>2+</sup> fluxes.<sup>181</sup> Many previous investigations have demonstrated that glucose homeostasis regulation using miR-375 can be mediated by taking into consideration modulation of the phosphatidylinositol 3-kinase (PI3K) signaling procedure in pancreatic  $\beta$  cells.<sup>182</sup> In pancreatic adenocarcinoma cells, expression levels of miR-375 were dramatically downregulated.<sup>183,184</sup> Hence, the accurate influence of the downregulation on the metabolism of glucose as well as the potential objectives have not been determined in the case of the tumor cells.

### Biogenesis of lncRNAs

lncRNAs play important roles in several human diseases and also in normal development.<sup>185,186</sup> An understanding of the biogenesis of lncRNAs has been very helpful for differentiating them from other types of ncRNAs, and also for deciphering their functional importance. The biogenesis of lncRNAs is cell stage- and cell type-dependent.<sup>187,188</sup> Many lncRNAs have been transcribed from DNA sequences, such as promoters, intergenic regions, and enhancer regions in eukaryotic genomes.<sup>189</sup> The first step involved in lncRNA biogenesis is cleavage by RNase P for generating mature ends. Most lncRNAs undergo 5' capping and 3' polyadenylation in the same way as mRNAs, but others have small nucleolar RNA (snoRNA) caps at the ends.<sup>190,191</sup> In recent years, sub-nuclear structures called "paraspeckles" about 200–1,000 nm in size have been identified between the chromatin structures. Paraspeckles consist of several proteins wrapped around a lncRNA core.<sup>192</sup> RNA interference (RNAi) evaluations of 40 paraspeckle proteins (PSPs) led to the identification of 4 PSPs that were essential for the formation of paraspeckles.<sup>193,194</sup> The mechanisms for formation and regulation of many lncRNAs are



**Figure 2. lncRNAs Regulate Some Molecules Involved in Glucose Metabolism in Cancer**

lncRNAs regulate glucose uptake and glycolytic flux by modulating GLUTs and glycolytic enzymes. This figure was adapted from Fan et al.<sup>200</sup>

not entirely understood. New techniques, such as chromatin isolation by RNA purification sequencing (ChIRP-seq), ribosome profiling, cross-linking immunoprecipitation (CLIP), phylogenetic lineage tracing, and RNA structure mapping using genetic screens and CRISPR, will provide much more information on the structure and function of lncRNAs.<sup>195–197</sup>

lncRNAs carry out regulatory functions because of their modular structure and RNA-DNA or RNA-RNA base pairing ability.<sup>20</sup> lncRNAs regulate gene function in several ways, including (1) recruitment of the chromatin remodeling complex to alter the chromatin organizational pattern; (2) acting as “sponges” by base pairing with miRNAs to reduce their effects; (3) providing docking sites for proteins that are located within the same pathway; (4) guiding certain transcription factors (TFs) to bind to the promoters; and (5) sequestering transcription factors and keeping them away from the promoters.<sup>196</sup>

#### Regulation of Glycolysis by lncRNAs

The lncRNA NBR2 regulates 5'-AMP-activated protein kinase (AMPK) activity under energy stress induced by glucose starvation. Liu and Gan<sup>198</sup> demonstrated that the knockout of NBR2 did not influence the activity of phenformin-induced AMPK, but it did decrease

the expression of GLUT1, thereby decreasing glucose utilization. The lncRNA called CRNDE (colorectal neoplasia differentially expressed) promotes colorectal cancer progression and drug resistance. The intron 4 of the gene contains a highly conserved sequence (gVC-In4). Ellis et al.<sup>199</sup> showed that in HT29 colorectal cancer cells, treatment with insulin or IGF inhibited transcription of CRNDE and gVC-In4. Knockout of gVC-In4 *in vitro* decreased the expression of genes involved in aerobic glycolysis and pyruvate conversion to acetyl-CoA, and it reduced the production of lactic acid. In addition, they found that the GLUT4 expression was decreased, showing that CRNDE positively regulates the GLUT4 level<sup>199</sup> (Figure 2).

Yiya is an lncRNA that was found to be upregulated in several cancers, and it is located on 1q41.<sup>201</sup> The expression of Yiya is associated with cell proliferation and cell cycle regulation.<sup>201</sup> Cyclin-dependent kinase 6 (CDK6) is considered a major regulator of the cell cycle and modulates several cell functions, although this is not completely understood.<sup>202</sup> When CDK6 was deleted in mice, they found disorders related to hematopoiesis.<sup>203</sup> According to some studies, CDK6 controls the PPP.<sup>204</sup> Small molecule inhibitors of CDK6 impaired PPP activity and lactate synthesis.<sup>204</sup> In one study, Xing et al.<sup>205</sup> assessed the effects of Yiya expression on glycolysis in breast cancer. Yiya was associated with cytosolic CDK6 and modulated CDK6-



dependent phosphorylation of the fructose bisphosphatase PFK2 (PFKFB3) enzyme, which mediates the conversion of glucose 6-phosphate to fructose-2,6-bisphosphate/fructose-1,6-bisphosphate. CDK6 silencing and CRISPR-Cas9-mediated suppression of *Yiya* inhibited glycolysis and tumor development. In 40% of breast cancer cases, the expression of *Yiya* was related to *CKD6* and a poor prognosis.<sup>205</sup>

NORAD (ncRNA activated by DNA damage) is also known as LOC647979 or LINC00657.<sup>206</sup> NORAD is known to be an oncogene and is implicated in breast cancer<sup>207</sup> and pancreatic cancer.<sup>208</sup> It is known that some lncRNAs can interact with miRNAs and act as RNA sponges that reduce their effect on the target mRNAs.<sup>209,210</sup> In pancreatic cancer, NORAD functions as a sponge for miR125a3p in order to modulate the Ras homolog family member A.<sup>208</sup> NORAD interacts with miR-202 and can promote the epithelial-mesenchymal transition, leading to metastasis and a poor prognosis in colorectal cancer.<sup>211</sup> NORAD is also highly expressed in non-small-cell lung cancer (NSCLC) and could be related to glycolysis and increased cell viability in lung cancer as reported by Gao et al.<sup>212</sup> These workers used quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) to investigate the expression of NORAD, miR136-5p, and markers of glycolysis and cell proliferation. The direct interaction of miR136-5p with NORAD was investigated using RNA immunoprecipitation and a luciferase reporter assay. NORAD was upregulated in NSCLC cell lines, and glycolysis and proliferation were also increased. They proposed that NORAD acted as a competing endogenous RNA for miR136-5p. Gain- and loss-of-function assays showed that miR136-5p reversed the effects of NORAD in lung cancer.<sup>212</sup>

MALAT1 (metastasis associated lung adenocarcinoma transcript 1) plays an oncogenic role in some cancers. For instance, Zhang et al.<sup>213</sup> showed that MALAT1 participates in renal cell carcinoma by modulation of the miR-203/BIRC5 axis. Sun et al.<sup>214</sup> also showed that MALAT1 was upregulated in ovarian cancer, and it played a role in apoptosis and proliferation by targeting miR503. Si et al.<sup>215</sup> reported that MALAT1 could suppress apoptosis and promote autophagy by sponging miR-101 in colorectal cancer. MALAT1 is highly expressed in multiple myeloma (MM),<sup>216</sup> and Liu et al.<sup>217</sup> reported that downregulation of MALAT1 by RNAi activated apoptosis and suppressed proliferation.

SRY-box 13 (SOX13) is a member of the Sry-related high-mobility group box (Sox) transcription factor family, and it has been implicated in some cancers, such as glioma<sup>218</sup> and gastric carcinoma.<sup>219</sup> Xu et al.<sup>220</sup> showed SOX13 was upregulated in MM.

Liu et al.<sup>221</sup> investigated the effects of MALAT1 on glycolysis in MM by measuring the expression levels of MALAT1, SOX13, and miR-1271-5p using quantitative real-time PCR. Flow cytometry, a transwell assay, and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were used to examine apoptosis, invasion, and cell viability, respectively. The lactate production, ATP/ADP ratio, related enzyme activities, and glucose consumption were examined to quantify glycolysis, plus western blotting for the related proteins. A dual-

luciferase reporter assay was used for understanding target interactions. An MM xenograft tumor model was carried out in mice. MALAT1 was overexpressed and miR-1271-5p was downregulated in MM cells. Deletion of MALAT1 inhibited invasion, glycolysis, and reduced cell viability. MALAT1 targeted miR-1271-5p, and SOX13 was shown to be a target of miR-1271-5p. MALAT1 regulated SOX13 by targeting miR-1271-5p. By downregulation of MALAT1, MM development and glycolysis were suppressed via the miR-1271-5p/SOX13 axis.<sup>221</sup>

Ftx (five prime to the X-inactivation center [XIST]) is located near XIST on the X chromosome.<sup>222</sup> Ftx encodes a transcript of 2,300 nt with nine introns, the second and seventh of which encode two clusters of miRNAs, that is, miR-545/miR-374a and miR-421/miR-374b. The other introns encode Ftx itself, so there are no overlaps between miRNAs and Ftx. lncRNA Ftx/miR-545 participates in tumorigenesis in hepatocellular carcinoma (HCC) by affecting the PI3K/RAC- $\alpha$  serine/threonine-protein kinase axis via targeting the DEXD/H-box helicase 58.<sup>223</sup> The relationship between glycolysis and Ftx is not yet clear.

Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) combines with PPAR elements to modulate the transcription of target genes, and it heterodimerizes with the retinoid X receptor. PPAR $\gamma$  has a role in steatosis-associated hepatic tumorigenesis,<sup>224</sup> and it is involved in cellular sensitivity to insulin and insulin resistance.<sup>225</sup> It has a role in the regulation of some enzymes in carbohydrate metabolism. For instance, it promotes GLUT4 expression<sup>226</sup> and suppresses PDK1 expression.<sup>227</sup> PPAR $\gamma$  was reported to reduce the production of leptin and tumor necrosis factor (TNF)- $\alpha$  and improve cellular sensitivity to insulin and facilitate glucose utilization.<sup>228</sup>

Li et al.<sup>229</sup> studied the role of Ftx in glycolysis in HCC. High expression levels of Ftx enhanced invasion, migration, and proliferation of HCC, while low expression of Ftx had the opposite effects. Ftx played a role in glycolysis, the expression of enzymes related to carbohydrate metabolism, glucose transporter expression, glucose consumption, and lactate production. PPAR $\gamma$  expression was related to the expression of Ftx in HCC. The inhibition of PPAR $\gamma$  using GW9662 in Huh7 HCC cells that overexpressed Ftx partially abrogated the increases in glucose uptake, lactate production, and relative glycolytic enzyme expression induced by Ftx. Conversely, in Bel-7402 HCC cells, activation of PPAR $\gamma$  rescued Ftx-mediated suppression of lactate production, glycolytic enzyme expression, and glucose uptake induced by Ftx.<sup>229</sup>

Proteins, lipids, and nucleotides derived from glycolytic metabolism are used for cell division and proliferation.<sup>38</sup> LDHA catalyzes the last step of the glycolysis pathway. Abnormal expression levels of LDHA have been found in some cancers such as pancreatic cancer,<sup>230</sup> HCC,<sup>231</sup> and breast cancer.<sup>232</sup> Suppression of LDHA decreases malignant transformation and delays tumor progression.<sup>4</sup> Studies have investigated the mechanisms of the suppression of tumor growth after LDHA inhibition.<sup>233,234</sup> Reduction of LDHA activity either by siRNA

or by a small molecule inhibitor altered energy metabolism and caused oxidative stress and cell death in lymphoma both *in vitro* and *in vivo*.<sup>233</sup> LDHA deletion inhibited tumorigenicity via stimulation of oxidative stress-mediated mitochondrial apoptosis in breast cancer.<sup>234</sup> In one study, Chen et al.<sup>235</sup> assessed the role of the lncRNA CRYBG3 on glycolysis in lung cancer. Overexpression of CRYBG3 stimulated glycolysis and enhanced glucose uptake and lactate production, while its deletion had the opposite effect.<sup>235</sup>

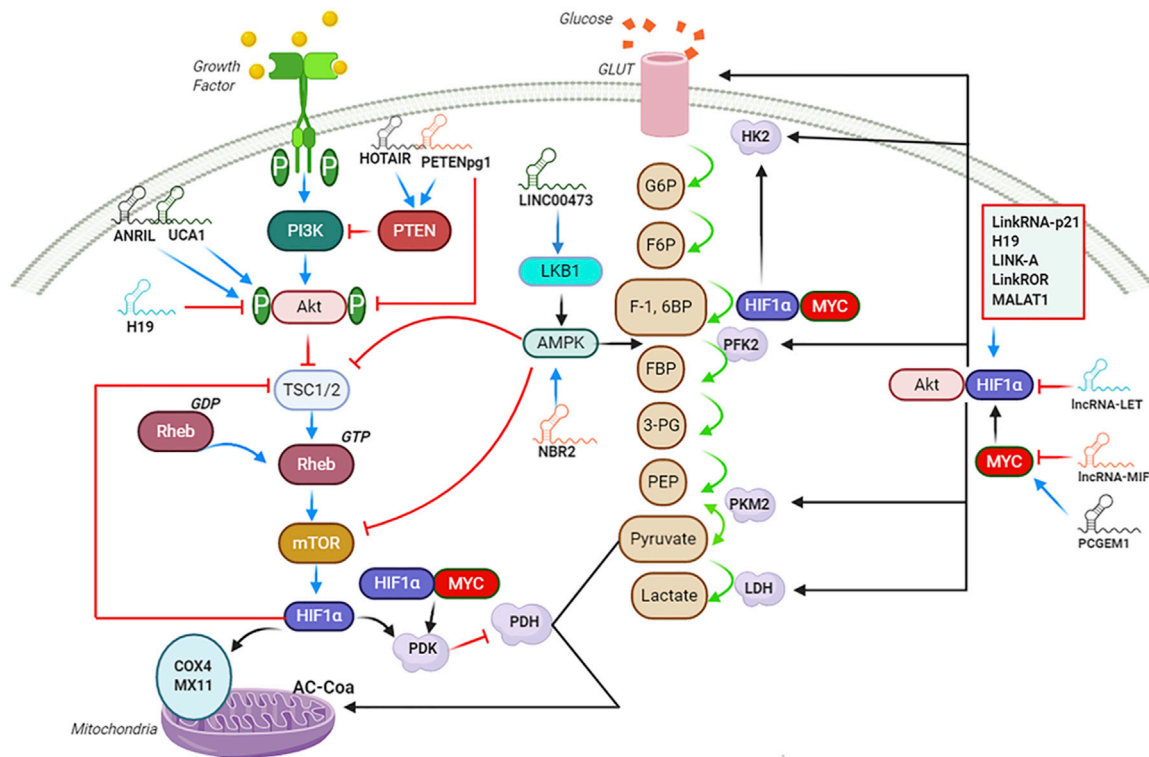
GLUT1 (also known as SLC2A1) is a transporter for glucose uptake, and it is expressed by cancer cells for rapid proliferation and energy production by glycolysis. SLC2A1 is highly expressed in lung cancer,<sup>236</sup> colon cancer,<sup>237</sup> and gastric cancer.<sup>97</sup> Chen et al.<sup>238</sup> showed that CREB (cyclic AMP [cAMP]-responsive element binding protein) affected glucose transport via modulating the expression of SLC2A1 and modulated the metabolism and progression of glioma. Shi et al.<sup>239</sup> investigated the effect of LINC00174 on glycolysis in glioma. *In situ* hybridization and quantitative RT-PCR were used to examine the expression of LINC00174 in glioma cell lines and samples. ELISA assays, a transwell invasion assay, scratch wound healing, TUNEL (terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick end labeling), and a Cell Counting Kit-8 (CCK-8) assay were used to examine the effects on glioma cells. Western blotting, RNA pull-down, dual-luciferase reporter, and RNA immunoprecipitation assays were performed to understand the mechanism. A nude mouse xenograft model was used to understand the role of LINC00174 in glioma development. LINC00174 was overexpressed in glioma tissues and cell lines. LINC00174 deletion suppressed glycolysis, proliferation, migration, and invasion and also affected glioma tumorigenesis. Suppression of miR-152-3p or overexpression of SLC2A1 could reverse the anti-tumor effects of LINC00174 deletion on glioma. Downregulation of LINC00174 reduced the tumor volume and delayed tumor development.<sup>239</sup>

Phosphatase and tensin homolog (PTEN) is known to function as a tumor inhibitor in some cancers, such as endometrial carcinoma, kidney cancer, and melanoma.<sup>240–242</sup> In esophageal squamous cell carcinoma (ESCC), epigenetic silencing of PTEN by promoter hypermethylation was shown to be a mechanism of PTEN reduction.<sup>243</sup> Li et al.<sup>244</sup> investigated the effects of LINC00184 on glycolysis in esophageal cancer. Quantitative RT-PCR was used to examine LINC00184, and it was found to be upregulated in ESCC, and at the same time PTEN was downregulated. Gain and loss of function was used to evaluate cellular processes *in vivo* and *in vitro*. Deletion of LINC00184 was found to suppress colony formation, proliferation, migration, and invasion, while glycolysis was reduced and mitochondrial OXPHOS was restored. LINC00184 promoted promoter methylation of PTEN by recruiting DNMT1. Suppression of PTEN promoter methylation increased mitochondrial OXPHOS while it inhibited glycolysis. LINC00184 was proposed to regulate glycolysis and mitochondrial OXPHOS in ESCC via Akt phosphorylation, and when Akt was inhibited by LY294002 the effects of LINC00184 on mitochondrial OXPHOS and glycolysis were reversed.<sup>244</sup>

The dysregulation of the oncogene *MYC* has been found to be a common event in tumorigenesis. *MYC* encodes a transcription factor, c-Myc, that stimulates proliferation and cell growth. Kim et al.<sup>245</sup> showed that HIF-1 could act cooperatively with dysregulated c-Myc to promote glycolysis in the P493-6 Burkitt's lymphoma model with an inducible *MYC*. The expression of the glycolysis enzyme hexokinase 2 was induced, and also pyruvate dehydrogenase kinase 1 that can inactivate pyruvate dehydrogenase and decrease mitochondrial respiration. The lncRNA PCGEM1 (prostate cancer gene expression marker 1) can affect many metabolic processes at the transcriptional level, such as the PPP, glucose metabolism, fatty acid biosynthesis, nucleic acid, and the tricarboxylic acid cycle. PCGEM1 was shown to directly interact with c-Myc, promote c-Myc chromatin recruitment, and bind to the promoters of target genes.<sup>246</sup> The effects of c-Myc on glycolytic gene expression can increase glucose metabolism under normal oxygen conditions. The c-Myc protein level can be decreased by the lncRNA MIF (c-Myc inhibitory factor), hence suppressing glycolysis. It was proposed that lncRNA-MIF works as an endogenous competitive RNA to sequester miR-586, thereby decreasing the inhibitory effect of miR-586 against Fbxw7 (F-box/WD repeat-containing protein 7). Fbxw7 is an E3 ubiquitin ligase that can reduce the stability of c-Myc protein. Therefore, lncRNA-MIF can increase the expression of Fbxw7 and reduce the level of c-Myc protein. As shown in Figure 3, there is a feedback loop between lncRNA-MIF and c-Myc that can regulate glucose metabolism and glycolysis.<sup>247</sup> Alternatively, the metabolic signaling pathways shown in Figure 3 do not completely reflect the current understanding of these complex networks. For example, the insulin receptor (IR) activates the PI3K/Akt signaling pathway, which is responsible for most of the metabolic activity of insulin. The IR has two splice isoforms, both of which can phosphorylate at least six known IR substrate (IRS) proteins. These IRSs are capable of interacting with eight known forms of the PI3K regulatory subunit. PI3K regulatory subunits, in turn, can associate with three forms of the PI3K catalytic subunit, and the products of PI3K enzyme activity can then activate three isoforms of Akt. The combinatorial possibilities of the IR/IRS/PI3K/Akt part of the insulin-signaling pathway alone exceed 1,000 combinations. When differential compartmentalization, stoichiometry, and the kinetics of the various downstream signaling components are taken into account, this number increases dramatically<sup>248</sup> (Table 2).

### circRNA Biogenesis

In eukaryotic cells, the processing of the exons of pre-mRNAs by alternative splicing can lead to linear mRNA sequences. circRNAs are produced by a different kind or aberrant RNA splicing in contrast to linear RNAs.<sup>274</sup> circRNAs are more resistant to degradation by RNase enzymes, and they have been found to be more stable compared to linear RNAs due to the presence of a covalent closed-loop structure.<sup>275</sup> Vo et al.<sup>26</sup> characterized circRNAs in more than 2,000 different cancer samples. They found a general reduction in the global abundance of circRNAs compared to the adjoining normal tissues. Many subtypes of circRNA have recently been characterized using next-generation technologies. There are now four recognized subtypes of circRNAs: (1) exonic circRNAs (ecircRNAs) derived from several or many single



**Figure 3. Role of PI3K/AKT/mTOR, LKB1-AMPK, and lncRNA-mediated HIF in Glucose Metabolism in Tumor Cells**

The stability and synthesis of HIF-1 $\alpha$  protein can be affected by lncRNAs, thus modulating HIF-1-mediated metabolic reprogramming. In cancer cells, the translation of HIF-1 $\alpha$  mRNA is dependent on the activity of the mammalian target of rapamycin (mTOR) governed by the activity of upstream tumor suppressor proteins and oncoproteins. HIF-1 $\alpha$  plays a key role in blocking mitochondrial activity and stimulating glycolytic enzymes. lncRNAs can also regulate the Akt and AMPK pathways. Akt may increase oxidative phosphorylation by enhancing metabolic coupling between glycolysis and oxidative phosphorylation, through facilitating the association of mitochondrial hexokinase with VDAC in the mitochondria. Akt enhances glycolytic flux via several mechanisms. First, it increases glucose uptake and flux. Second, hyperactivated Akt activates mTORC1, which promotes HIF-1 $\alpha$  accumulation under normoxic conditions and increases levels of GLUT1, HKII, and lactate dehydrogenase (LDH). Finally, Akt-increased cellular ATP levels help to maintain low AMPK activity, which is required for full activation of mTORC1. This figure was adapted from Fan et al.<sup>200</sup>

exons; (2) circular intronic RNAs (ciRNAs) derived only from introns; (3) exonic-intronic circRNAs (EIciRNAs), including both exons and introns; and (4) tRNA intronic circRNAs (tricRNAs) created by the splicing of pre-tRNA introns. Recently, most of the sequenced circRNAs have been determined to be ecircRNAs. The biogenesis mechanisms of circRNAs depend on the particular sub-type. ecircRNAs are produced by back splicing and lariat-driven circularization. In the lariat, the existing introns are removed, and the exons are linked together by a 5'-3' phosphodiester bond. The downstream donor and the upstream splice acceptor sites are then closed in a circle to create a lariat, which includes the exons.<sup>276</sup> In the downstream and upstream introns, interactions occur with RNA-binding proteins (RBPs) to form a "bridge," followed by back splicing for the formation of the ecircRNAs.<sup>277,278</sup> In base pairing-driven circularization of ecircRNAs, the downstream splicing donor site can be linked to the upstream splicing receptor site based on ALU complementary sequences. The introns can either be removed or maintained to produce both EIciRNAs or ecircRNAs.<sup>275</sup> The biosynthesis of ciRNAs is mainly based on an 11-nt C-rich sequence and a 7-nt GU-rich element for directing the sites of exonucleolytic cleavage and debranching degradation.<sup>279</sup> EIciRNAs

and ciRNAs are located within the nucleus where they play role in controlling parental gene transcription, in contrast to ecircRNAs, which are localized within the cytoplasm. tricRNA is a particular intronic circRNA found in Archaea and *Drosophila* species.<sup>280-282</sup> The formation of tricRNA requires the activity of tRNA splicing enzymes to divide the pre-tRNA into two different sections. One of these sections produces tRNAs, while tricRNAs are produced from the other section by formation of a 3'-5' phosphodiester bond.<sup>281</sup> It is accepted that the binding of RNA proteins and the presence of particular repetitive sequences surrounding the introns and the circularized exons govern the formation of circRNAs.

The mechanisms of how circRNAs regulate gene function have been investigated in several studies, leading to three main possibilities.<sup>277,283</sup> (1) circRNAs often have miRNA binding sites that allow them to bind to miRNAs, acting as a "miRNA sponge" in order to inhibit miRNA binding to the target mRNAs. (2) circRNAs can also interact with RBPs, which leads to the depletion of RBPs and thus reduces their interaction with RNA targets. (3) It has been suggested that the circRNAs that are generated by circularization of exons might compete with the splicing of

**Table 2. Selected lncRNAs Involved in the Regulation of Glycolysis in Various Cancers**

Cancer	lncRNAs	Expression in Cancer	Target	Model	Samples	References
Pancreatic ductal adenocarcinoma	PVT1	upregulation	HIF-1 $\alpha$	<i>in vitro, in vivo, human</i>		249
Hepatocellular carcinoma	SLC2A1-AS1	downregulation	STAT3/FOXM1/GLUT1 pathway	<i>in vitro, in vivo, human</i>	33	250
	LINC01554	downregulation	PKM2, Akt/mTOR signaling pathway	<i>in vitro, in vivo, human</i>	167	251
	HOTAIR	upregulation	HIF-1 $\alpha$	<i>in vitro, human</i>	38	252
Colorectal cancer	HNF1A-AS1	upregulation	MYO6	<i>in vitro, human</i>	40	253
	LINRIS	upregulation	IGF2BP2	<i>in vitro, in vivo, human</i>		254
	MAFG-AS1	upregulation	NDUFA4	<i>in vitro, in vivo, human</i>	52	255
	GLCC1	upregulation	LDHA	<i>in vitro, in vivo, human</i>	40	256
Non-small-cell lung cancer	BCYRN1	upregulation	PKM2	<i>in vitro, human</i>	20	257
	LINK-A	upregulation	HKII	<i>in vitro, in vivo, human</i>	113	258
	LINC00243	upregulation	PDK4	<i>in vitro, human</i>	70	259
	HOTTIP	upregulation	HMGB3	<i>in vitro</i>		260
Multiple myeloma	MALAT1	upregulation	SOX13	<i>in vitro, in vivo, human</i>	30	261
Endometrial carcinoma	SNHG16	upregulation	HK2	<i>in vitro, in vivo, human</i>		262
Glioma	LINC00174	upregulation	SLC2A1	<i>in vitro, in vivo, human</i>	45	239
	LINC00689	upregulation	PKM2	<i>in vitro, in vivo, human</i>	56	263
Esophageal cancer	LINC00184	upregulation	PTEN	<i>in vitro, human</i>	84	244
Cervical cancer	UCA1	upregulation	HK2	<i>in vitro, human</i>		264
Breast cancer	YIYA	upregulation	CDK6	<i>in vitro, human</i>		205
	MEG3	downregulation	PI3K/Akt pathway	<i>in vitro, in vivo, human</i>	20	265
Ovarian cancer, CAFs	LINC00092	upregulation	CXCL14	<i>in vitro, in vivo, human</i>	58	266
Nasopharyngeal carcinoma	ANRIL	upregulation	mTOR signaling pathway	<i>in vitro, human</i>	88	267
Lung cancer	IGFBP4-1	upregulation	HK2, PDK1, LDHA	<i>in vitro, in vivo, human</i>	159	268
Papillary thyroid carcinoma	ASMTL-AS1	downregulation	FOXO1	<i>in vitro, in vivo, human</i>	95	269
Ovarian cancer	LINC00504	upregulation	PKM2, HK2, PDK1	<i>in vitro, human</i>	45	270
Oral squamous cell carcinoma	p23154	upregulation	GLUT1	<i>in vitro, in vivo, human</i>	49	271
Pediatric acute myeloid leukemia	UCA1	upregulation	hexokinase 2 pathway	<i>in vitro, human</i>	31	272
Osteosarcoma	PVT1	upregulation	HK2	<i>in vitro, human</i>	46	273

CAF, cancer-associated fibroblast.

pre-mRNA into linear RNA, because they act on the same splice sites. Therefore, the mRNAs might lack the exons that were present in the circRNA, thus altering the composition of the mRNAs.<sup>284</sup>

### Regulation of Glycolysis by circRNAs

As mentioned above, circRNAs have been found to be widespread and involved in many developmental steps as well as normal physiological conditions using high-throughput deep RNA sequencing as well as bioinformatics technology.<sup>275,285</sup> Naturally occurring circRNAs play an important role in the interaction network of RNA. circRNAs are relatively stable, diverse, extremely abundant, and highly conserved.<sup>275</sup> circRNAs are involved in processes such as controlling the expression of parental genes, acting as endogenous RNAs to sponge miRNAs, regulating RNA-protein interactions and functioning as scaffolds for the assembly of protein complexes, as well as modulating alternative splicing.<sup>286,287</sup>

It has also been discovered that circRNAs are involved in the pathogenesis of many human diseases, including cardiovascular disorders,<sup>288</sup> nervous system disorders,<sup>289</sup> osteoarthritis,<sup>290</sup> diabetes,<sup>291</sup> Alzheimer's disease, silicosis,<sup>292</sup> and cancer.<sup>293,294</sup> circRNAs have important roles in the growth of cancer, stemness of the malignant cells, metastasis, and treatment resistance.<sup>295,296</sup>

There is one circRNA, named circMYC (hsa\_circ\_0085533), that has been found in HepG2 cancer cells, HeLa S3 cells, normal human epidermal keratinocytes, and human lung fibroblasts. It is located on chromosome 8 with a 555-base genomic length.<sup>285</sup> circMYC is highly expressed in melanoma and is related to tumorigenesis. LDHA changes pyruvate into lactate and is one of the hallmarks of cancers.<sup>297</sup> LDHA is considered a valid therapeutic target in many cancers, such as pancreatic cancer, lymphoma, and lung, liver, and breast cancers. Increased LDHA activity and lactate production are



**Table 3. Selected Circular RNAs Involved in the Regulation of Glycolysis in Various Cancers**

Cancer	Circular RNAs	Expression in Cancer	Target	Model	Samples	Reference
Melanoma	circMYC	upregulation	3' UTR of LDHA	<i>in vitro</i> , human	25	<sup>311</sup>
Non-small-cell lung carcinoma	circACACA	upregulation	PI3K/PKB pathway	<i>in vitro</i> , <i>in vivo</i> , human		<sup>312</sup>
Lung cancer	circAKT3	upregulation	STAT3	<i>in vitro</i> , <i>in vivo</i> , human	28	<sup>313</sup>

associated with poor prognosis and resistance to chemotherapy and radiotherapy.<sup>231,234,298,299</sup> LDHA was found to be overexpressed in nevic melanocytes and primary and metastatic melanomas.<sup>300</sup> In one study, Jin et al.<sup>301</sup> assessed the effect of circMYC on glycolysis in melanoma. circMYC increased the proliferation in Mel-CV cells and human melanoma cells. Overexpression of circMYC led to inhibition of LDHA activity and lower glycolysis. circMYC targeted miR-1236 and bound to it as a molecular sponge.<sup>301</sup>

The PI3K/protein kinase B (PKB) signaling pathway is critical for cell apoptosis and survival.<sup>302</sup> It has been proposed that some cancers are related to the incorrect activation of that pathway.<sup>303</sup> The PI3K/PKB signaling pathway was implicated in the initiation of endometrial cancer<sup>304</sup> and cisplatin (DDP) resistance in lung cancer.<sup>305</sup> Understanding of the PI3K/PKB pathway could help to improve therapies for lung cancer.

Wu et al.<sup>306</sup> studied the effects of circACACA on glycolysis in NSCLC. qPCR was used to measure the expression of miR-1183 and the circACACA Transwell assay, and CCK-8 assays were used to measure migration and proliferation. The Seahorse XFe96 analyzer was used to study mitochondrial metabolism, and western blotting was used to quantify the expression of GLUT1, matrix metalloproteinase 9, c-Myc protein, PTEN, phosphorylated (p-)PI3K, PKB, p-PKB, and PI3K. An RNA pull-down assay, RNA immunoprecipitation assay, and dual-luciferase reporter assays were used to study the correlation between circACACA and miR-1183. A xenograft tumor model was used to understand the biological role of circACACA. circACACA was highly expressed in NSCLC samples and cell lines, and the pattern was the opposite of miR-1183 expression. Deletion of circACACA suppressed glycolysis, proliferation, and migration in NSCLC. miR-1183 was targeted by circACACA, and circACACA modulated the PI3K/PKB signaling pathway by interacting with miR-1183. Reducing the expression of circACACA inhibited tumor development.<sup>306</sup>

Signal transducer and activator of transcription 3 (STAT3) has a role in ischemic cardiac hypertrophy and tumor-associated macrophage differentiation.<sup>307,308</sup> Dong et al.<sup>309</sup> showed that circ\_0076305 regulated DDP resistance in NSCLC by positively modulating STAT3 via sponging of miR-296-5p. Xu et al.<sup>310</sup> investigated the effects of circAKT3 on glycolysis in NSCLC. Western blotting and quantitative real-time PCR were used to examine the expression of miR-516b-5p, circAKT3, and STAT3 in NSCLC. MTT was used to measure the sensitivity to DDP. For measuring the lactate production and glycolysis in cells treated with different plasmids or 2-deoxy-glucose

(2-DG), a lactate assay and glucose assay kits were used. The expression of HIF-1 $\alpha$  in H1299 and A549 cells was detected by western blotting. Relationships between circAKT3, miR-516b-5p, and STAT3 were studied using a dual-luciferase reporter assay. circAKT3 and STAT3 were highly expressed in lung cancer while miR-516b-5p showed low expression. Deletion of circAKT3 inhibited glycolysis and increased the sensitivity to DDP. In A549 cells, the inhibition of HIF-1 $\alpha$ -induced glycolysis abrogated the circAKT3-induced chemoresistance. miR-516b-5p was found to bind to circAKT3. Suppression of miR-516b-5p reversed the effects of circAKT3 deletion on glycolysis, as well as DDP sensitivity. Deletion of circAKT3 inhibited development of tumors *in vivo* by the miR-516b-5p/STAT3 axis<sup>310</sup> (Table 3).

## Conclusions

Cancer is a complex disease at the cellular level, whose causative factors include environmentally induced mutations, heritable genetic conditions, and epigenetic alterations. Cancer cells are further required to modulate their metabolism in accord with the tumor microenvironment in order to survive and proliferate under the conditions imposed on them by the unrestricted growth of the tumor. The metabolic reprogramming that occurs in tumors to support cell expansion and proliferation is facilitated by the loss of tumor suppressor proteins or the activation of oncogenes. In recent times, a large number of different ncRNAs have been discovered, and these are now accepted as major mechanisms of epigenetic control of gene expression. Many ncRNAs have been implicated in the initiation, progression, and metastatic spread of different types of cancer. The dysregulated metabolism in cancer cells (called the Warburg effect) relies on switching energy production away from OXPHOS toward aerobic glycolysis. Several different sub-types of ncRNAs, including miRNAs, lncRNAs, and circRNAs, have been found to play regulatory roles in cancer metabolism, particularly in mitochondrial functions, and in the metabolism of lipids, glucose, and glutamine. Many ncRNAs have been implicated in cancer metabolic reprogramming and the switch to glycolysis, thus increasing the overall aggressiveness of the tumor. Not only could further investigations into the mechanisms and functions of ncRNAs allow the discovery of additional prognostic biomarkers, but they could also be beneficial for the development of novel therapeutic approaches.

## AUTHOR CONTRIBUTIONS

H.M. and M.R.H. contributed to the conception, design, data collection, and drafting of the manuscript. Both authors approved the final version for submission.



## CONFLICTS OF INTEREST

M.R.H. declares the following potential conflicts of interest: Scientific Advisory Boards: Transdermal Cap, Cleveland, OH, USA; BeWell Global, Wan Chai, Hong Kong; Hologenix, Santa Monica, CA, USA; LumiThera, Poulsbo, WA, USA; Vielight, Toronto, ON, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics, Cambridge, MA, USA; Global Photon, Bee Cave, TX, USA; Medical Coherence, Boston MA, USA; NeuroThera, Newark, DE, USA; JOOVV, Minneapolis-St. Paul, MN, USA; AIRx Medical, Pleasanton, CA, USA; FIR Industries, Ramsey, NJ, USA; UVLRx Therapeutics, Oldsmar, FL, USA; Ultralux UV, Lansing, MI, USA; Illumiheal & Pether, Shoreline, WA, USA; MB Lasertherapy, Houston, TX, USA; ARRC LED, San Clemente, CA, USA; Varuna Biomedical, Incline Village, NV, USA; and Niraxx Light Therapeutics, Boston, MA, USA. Consulting: Lexington International, Boca Raton, FL, USA; USHIO, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland BV, Eindhoven, the Netherlands; Johnson & Johnson, Philadelphia, PA, USA; and Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stock holdings: Global Photon, Bee Cave, TX, USA; and Mitonix, Newark, DE, USA. H.M. declares no competing interests.

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