


# Regulatory Mechanisms of LncRNAs in Cancer Glycolysis: Facts and Perspectives

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**Abstract:** Cancer cells exhibit distinct metabolic characteristics that employ glycolysis to provide energy and intermediary metabolites. This aberrant metabolic phenotype favors cancer progression. LncRNAs are transcripts longer than 200 nucleotides that do not encode proteins. LncRNAs contribute to cancer progression and therapeutic resistance and affect aerobic glycolysis via multiple mechanisms, including modulating glycolytic transporters and enzymes. Further, dysregulated signaling pathways are vital for glycolysis. In this review, we highlight regulatory mechanisms for LncRNAs in aerobic glycolysis that provide novel insights into cancer development. Moreover, a comprehensive understanding of the regulatory mechanisms of LncRNAs in aerobic glycolysis can provide new strategies for clinical cancer management.

**Keywords:** lncRNA, cancer progression, glycolysis, signaling pathway

## Introduction

Metabolism consists of multiple interconnected cellular chemical transformations that provide energy to sustain life.<sup>1</sup> Cancer is a malignant disease characterized by infinite proliferation.<sup>2</sup> To satisfy the increasing energy demands and biomass, cancer cells show metabolic plasticity to reprogram the metabolic pathways that include the metabolism of glucose, glutamine and fatty acids.<sup>3</sup> Among these, aberrant glucose metabolism is one well-known metabolic reprogramming in cancer. While most normal cells depend primarily on mitochondrial oxidative metabolism to generate energy, cancer cells employ glycolysis to provide energy and intermediary metabolites, even under aerobic conditions. This phenomenon was discovered by Warburg in the 1920s and is termed the Warburg effect or aerobic glycolysis.<sup>4</sup> The process often leads to enhanced glucose uptake, faster adenosine triphosphate (ATP) production and the accumulation of lactate in tumor cells, all of which are essential for tumorigenesis.<sup>5</sup> Enhanced glycolysis provides energy for accelerated proliferation,<sup>6</sup> and establishes an acidic microenvironment that promotes tumor cell invasion and metastasis.<sup>7</sup> Further, enhanced glycolysis helps tumor cells resist adjuvant therapy.<sup>8</sup> Therefore, glycolysis favors cancer cell survival under cellular stress conditions. However, mechanisms of the phenomenon await further investigation.

Non-coding RNAs (ncRNAs) are functional RNA transcripts that have no ability to encode peptides.<sup>9</sup> ncRNAs can be divided into two categories based on their length: short ncRNAs and long ncRNAs (lncRNAs). Short ncRNAs contain less than 200 nucleotides including microRNAs (miRNAs), small interfering RNAs

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(siRNAs), and small nuclear RNAs.<sup>9</sup> Conversely, lncRNAs are a novel group of regulatory RNA molecules that are more than 200 nucleotides in length.<sup>10</sup> Moreover, circular RNAs (circRNAs) are a novel type of ncRNAs. Unlike other RNA molecules, circRNAs have covalently closed circular structures.<sup>11</sup>

As a special type of ncRNAs, lncRNAs play a pivotal role in regulating gene expression through multiple mechanisms, such as remodeling chromatin structure, regulating DNA methylation, and transcriptional activation or interference.<sup>12</sup> They are also implicated in post-transcriptional modulation of gene expression via regulating mRNA processing. Further, they are closely correlated with post-translational modification of proteins, including phosphorylation and ubiquitination.<sup>12</sup> LncRNAs also act as molecular sponges of miRNAs to modulate target gene expression and may function as precursors for miRNAs or siRNAs.<sup>12</sup> Finally, lncRNA also regulate alternative splicing processes that contribute to the spatial and temporal expression of genes.<sup>12</sup>

LncRNAs regulate cancer cell proliferation, invasion, metastasis, and therapeutic resistance. Such activities are partially dependent on their ability to regulate aerobic glycolysis.<sup>13–16</sup> These molecules regulate glycolytic transporters and metabolic enzymes, thus interfering with metabolic signaling pathways. Underlying mechanisms of lncRNAs function in aerobic glycolysis are complicated and await systematic and comprehensive research. In this review, we highlight molecular mechanisms by which lncRNAs modulate aerobic glycolysis. Also, the potential therapeutic role of lncRNAs in aerobic glycolysis is discussed. Understanding these processes may support a comprehensive theoretical basis for clinical cancer management.

## Overview of Glycolysis in Cancer Glycolysis in Cancer Progression

Tumor cells exist in an unfavorable microenvironment that is hypoxic, acidic, and nutrient deficient. As an adaptive mechanism, tumor masses exhibit remarkable plasticity in converting to aerobic glycolysis.<sup>17,18</sup> This specific metabolic reprogramming allows infinite proliferation of cancer cells.

Glycolysis is an inefficient way to provide energy but maintains rapid ATP production under energy stress. The rapid ATP production is required for cell proliferation.<sup>19</sup> Additionally, glycolytic metabolism supplies large

quantities of building blocks for biosynthesis in proliferating cancer cells. Activated glycolytic flux accompanied by 3-phosphoglycerate and dihydroxyacetone phosphate production sustains the production of amino acids, triglycerides, and phospholipids needed to accelerate proliferation.<sup>6</sup> Under energy stress, enhanced glycolysis also favors tumor survival. Glycolysis produces fewer reactive oxygen species (ROS) than mitochondrial oxidative metabolism, reducing senescence and apoptosis.<sup>6</sup>

Cancer cells are apt to metastasize to remote sites to escape energy restrictions in primary tumor tissues. The glycolytic phenotype is advantageous for invasion and metastasis.<sup>7</sup> Excessive lactic acid production by aerobic glycolysis generates higher hydrogen ion concentration (lower pH), thereby establishing an acidic extracellular environment. This environment favors degradation of extracellular matrices and enhances metastasis by inducing metalloproteinases.<sup>20</sup> The acidic environment also sustains metastasis by helping cancer cells evade immune surveillance.<sup>21</sup> Moreover, aerobic glycolysis reduces ROS production and increases antioxidant activity in cancer cells. These changes confer resistance to anoikis and enable distant metastasis.<sup>22</sup>

## Glycolysis and Cancer Therapeutic Resistance

Cancer cell survival under altered glucose metabolism is a pivotal phase in oncogenesis and the development of treatment resistance.<sup>23</sup> Adjuvant chemotherapy is the primary treatment for cancers; resistance of cancer cells to chemical agents significantly reduces survival of cancer patients.<sup>24</sup> Theoretically, a tumor mass, composed of distinct chemo-resistant cells, is vital for chemoresistance.<sup>25</sup> Actually, suppression of glycolysis inhibits cell proliferation and reduces resistance to anticancer drugs.<sup>5</sup> In hepatocellular carcinoma (HCC) cells, enhanced aerobic glycolysis promotes sorafenib-resistance, and suppression of glycolysis reverses this resistance.<sup>26</sup>

Radiotherapy is also used to treat cancers. Radiation can kill cancer cells through breaking DNA double-strands and can thus prolong the survival of cancer patients and improve their quality of life.<sup>27</sup> Glycolysis generates a chemically reduced milieu that favors development of radio-resistance in multiple types of cancer cells, including colorectal and breast cancer and melanoma.<sup>28–30</sup> For example, activation of AKT enhances aerobic glycolysis and may induce acquired radio-resistance in human cancer cells.<sup>31</sup>

Adoptive T cell therapy (ACT) is a personalized and innovative immunotherapy strategy for cancer treatment. ACT uses transfusion of ex vivo-expanded autologous tumor-infiltrating lymphocytes into patients to regress tumors.<sup>32</sup> Unfortunately, many patients show regrowth of tumors because of acquired ACT resistance.<sup>33</sup> Cascone et al found that enhanced glycolysis attenuates the effectiveness of ACT, while repression of glycolysis promotes antitumor activity both in vivo and in vitro. Further, tumor cells from ACT-refractory melanoma patients display enhanced glycolytic metabolism compared with ACT responding patients.<sup>34</sup> Thus, glycolysis may be a crucial regulator of ACT resistance. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade may inhibit immunosuppression of activation of naive T cells by CTLA-4, thus obstructing tumor development.<sup>35,36</sup> Zappasodi et al showed that CTLA-4 blockade increases the number of infiltrating immune cells in glycolysis-deficient tumors. Additionally, CTLA-4 blockade enhances therapeutic activity against glycolysis-defective tumors in mice, suggesting that inhibition of tumor glycolysis may be effective for improving the therapeutic effects of CTLA-4 blockade.<sup>37</sup>

Overall, aerobic glycolysis is an optimal strategy for tumor cell survival in stressful microenvironments. It supports continued cell proliferation, growth, and metastasis and enhances resistance to antitumor treatment. However, the current understanding of aerobic glycolysis remains limited, which impedes the development of more effective cancer therapy. Understanding regulatory mechanisms of cancer glycolysis is thus significant and essential.

## Regulatory Mechanisms of LncRNAs in Cancer Glycolysis

Cancer cells are known for accelerated energy metabolism and enhanced glycolysis.<sup>6</sup> Altered glycolysis supplies energy for proliferation and influences cancer progression.<sup>38</sup> In this section, we summarize the regulatory mechanisms of lncRNAs regulation of glycolysis via altering the expression of glycolytic enzymes and transporters. Such transporters include glucose transporters (GLUTs) and monocarboxylate transporters (MCTs). The actions of lncRNAs in control of carcinogenesis and cancer progression via regulation of transporters and glycolytic enzymes are summarized in Table 1.

## LncRNAs-Mediated Regulatory Mechanisms of Glycolytic Transporters GLUTs and GLUTs

GLUTs are important membrane proteins responsible for transporting glucose. These proteins play a critical role in regulating glucose homeostasis and metabolism.<sup>39</sup> Three GLUTs family members are involved in cancer glucose metabolism—GLUT1, GLUT3, and GLUT4.<sup>40,41</sup> GLUT1 is widely expressed in multiple tissues and participates in the regulation of basal glucose uptake.<sup>42</sup> GLUT3 is mainly expressed in nerve tissues, while GLUT4 is an important glucose metabolism regulator in skeletal muscle and adipose tissues.<sup>43</sup> However, GLUT4 is regulated by insulin, whereas the activity of GLUT1 and GLUT3 is not related to insulin.<sup>44</sup> Under physiological conditions, GLUTs transport glucose into cells to meet energy requirements. However, during tumorigenesis, GLUTs expression are often deregulated.<sup>40</sup> GLUT1 and GLUT3 are upregulated in multiple types of cancer.<sup>40</sup> Upregulated GLUT1 and GLUT3 promote glucose uptake, cancer metastasis and growth.<sup>45,46</sup> Moreover, GLUT4 is also upregulated in various cancers, leading to elevated glucose uptake and enhanced cancer progression.<sup>47,48</sup> Several lncRNAs affect glucose uptake by regulating GLUT expression or distribution.

LncRNA colorectal neoplasia differentially expressed (CRNDE) shows increased glucose uptake by enhancing the expression of GLUT4.<sup>49</sup> In oral squamous cell carcinoma (OSCC), a novel lncRNA-p23154, enhances glucose uptake and glycolysis through upregulating GLUT1. This upregulation promotes cell invasion and metastasis.<sup>50</sup> Moreover, lncRNA Neighboring Enhancer of FOXA2 (NEF) downregulates GLUT1 expression, resulting in less glucose uptake and reduced cell proliferation in non-small-cell lung cancer (NSCLC).<sup>51</sup> Further, overexpression of lncRNA mortal obligate RNA transcript (MORT) inhibits cell proliferation and glucose uptake in prostate carcinoma. GLUT1 overexpression reverses this anticancer function of MORT, lncRNA MORT/GLUT1 may play a crucial role in prostate carcinoma.<sup>52</sup>

MiRNAs are small RNA molecules of approximately 22 nucleotides that are important in physiological or pathological processes via negative regulation of mRNA expression.<sup>53</sup> LncRNA may function as competitive endogenous RNA (ceRNA), bind with miRNA, and alter target gene expression.<sup>54</sup> This ceRNA mechanism is correlated with GLUT-mediated glycolysis. For example, dopamine  $\beta$

**Table 1** The Regulatory Mechanisms of lncRNAs in Aerobic Glycolysis

lncRNA	Expression	Cancer Type	Functions and Targets	Reference
CRNDE	Up	CRC	Upregulates GLUT4; increases glucose uptake	[49]
p23154	Up	OSCC	Upregulates GLUT1; enhances glycolysis; promotes metastasis and invasion	[50]
NEF	Down	NSCLC	Downregulates GLUT1; reduces glucose uptake and cell proliferation	[51]
MORT	Down	Prostate carcinoma	Downregulates GLUT1; promotes cell proliferation and glucose uptake	[52]
DBH-ASI	Up	Melanoma	CeRNA for miR-223-3p; increases GLUT1 expression; facilitates cell proliferation and metastasis	[55]
MACC1-ASI	Up	Gastric cancer	Promotes the translocation of GLUT1 to the cell membrane; enhances glycolysis and glucose uptake; promotes cancer progression	[57]
SLC16A1-ASI	Up	Bladder cancer	Binds with E2F1 to co-activate the MCT1; promotes aerobic glycolysis and tumorigenesis	[59]
HOTAIR	Up	Pancreatic adenocarcinoma	Activates HK2 at the transcriptional level; promotes cell proliferation and glycolysis	[65]
NRCP	Up	Ovarian cancer	Acts as an intermediate binding partner between RNA polymerase II and STAT1; increases glucose-6-phosphate isomerase, ALDOA and ALDOC expression; promotes glycolysis and tumor growth	[66]
IGFBP4-1	Up	NSCLC	Increases HK2 and LDHA expression at the transcriptional level; promotes glycolysis and tumor growth	[67]
SNHG6	Up	CRC	Promotes the proportion of PKM2/PKM1 through alternative splicing; promotes glycolysis and tumor growth	[70]
HOXB-AS3	Down	Colon cancer	Encodes a peptide that inhibits the expression of PKM2; inhibits glycolysis and tumor growth	[72]
DLX6-ASI	Up	Gastric cancer	CeRNA for miR-4290; increases PDK1 expression; promotes glycolysis and cancer progression	[73]
KCNQ1OT1	Up	Osteosarcoma	CeRNA for miR-34c-5p; increases ALDOA expression; promotes glycolysis and tumor growth	[74]
WFDC2IP	Down	HCC	Transcriptionally activated by Nur77; inhibits the catalytic activity of PFKP and blocks the nuclear localization of PKM2 to suppress its transcriptional activity; inhibits glycolysis and hepatocarcinogenesis	[75,76]
HULC	Up	HCC	Enhances the phosphorylation of the LDHA and PKM2; promotes glycolysis and cell proliferation	[77]
YIYA	Up	Breast cancer	Promotes the CDK6 dependent phosphorylation of PFKFB3; promotes glycolysis and tumor growth	[78]
FEZF1-ASI	Up	CRC	Inhibits the ubiquitin-mediated degradation of PKM2; promotes glycolysis and cancer metastasis	[80]
LINC00470	Up	Glioblastoma	Promotes the phosphorylation of AKT; inhibits HK1 ubiquitinate-mediated degradation; enhances aerobic glycolysis and carcinogenesis	[81]
HIFAL	Up	Breast cancer	Recruits the PHD3 to hydroxylate PKM2; drives the nuclear translocation of hydroxyl-PKM2/PHD3 complex by hnRNPF; promotes aerobic glycolysis and tumor growth	[82]

(Continued)

Table 1 (Continued).

LncRNA	Expression	Cancer Type	Functions and Targets	Reference
PCED1B-ASI	Up	Glioblastoma	Promotes the translation of HIF-1 $\alpha$ mRNA; facilitates glycolysis and carcinogenesis	[85]
MIR210HG	Up	TNBC	Increases the HIF-1 $\alpha$ protein level; enhances the expression of LDHA, PKM2 and GLUT1; promotes glycolysis and tumor growth	[86]
LincRNA-p21	Up	Various cancers	Inhibits the degradation of HIF-1 $\alpha$ ; activates GLUT1 and LDHA; promotes Warburg effect	[88]
LINK-A	Up	TNBC	Prevents the degradation of HIF-1 $\alpha$ ; recruits LRRK2 to phosphorylate HIF-1 $\alpha$ , which promotes Warburg effect	[89]
PCGEM1	Up	Prostate cancer	Promotes the transcriptional activation of c-Myc on metabolic genes through enhancing histone H3 and H4 acetylation	[92]
GLCC1	Up	CRC	Strengthens the interaction between HSP90 and USP22, which stabilizes c-Myc; transcriptionally activates LDHA; promotes glycolysis and cell proliferation	[93]
IDHI-ASI	Down	Various cancers	c-Myc stabilizes HIF-1 $\alpha$ through IDHI-ASI/IDHI- $\alpha$ KG/ROS-HIF1 $\alpha$ pathway, which promotes aerobic glycolysis	[95]
LINC00184	Up	Esophageal cancer	Recruits DNMT1 to the promoter of PTEN to inhibiting its expression; promotes glycolysis	[101]
ANRIL	Up	Nasopharyngeal carcinoma	Activates AKT/mTOR signaling to upregulate GLUT-1, resulting in enhanced glycolysis	[102]
UCA1	Up	Bladder cancer	Activates mTOR to upregulate HK2 via both activating STAT3 and inhibiting miR-143; facilitates aerobic glycolysis	[103]
LINC01554	Down	HCC	Inactivates AKT/mTOR signaling pathway; abolishes tumorigenicity and aerobic glycolysis	[104]
XIST	Up	Glioblastoma	CeRNA for miR-126; promotes glycolysis via IRS1/PI3K/Akt/GLUT pathway	[106]
LINC00473	Up	NSCLC	Induced by LKB1 loss; interacts with NONO; promotes tumor growth	[115,116]
NBR2	Down	Various cancers	Potentiates AMPK activation; inhibits GLUT-1 expression; inhibits EMT and glycolysis.	[117,118]
MALAT1	Up	HCC	Inhibits p53 pathway; promotes tumor growth	[123]
MEG3	Down	Breast cancer	Promotes p53 pathway; inhibits tumor growth	[124,125]
SNHG9	Up	Glioblastoma	Promotes glycolytic metabolism and cell growth by downregulating miR-199a-5p and upregulating Wnt2	[128]
SNHG3	Up	Laryngeal squamous cell carcinoma	Promotes glycolysis and tumor growth by abolishing Wnt pathway via modulating the miR-340-5p/ YAP1 axis	[129]
LINC00857	Up	Ovarian cancer	Promotes ovarian cancer glycolysis through inactivating Hippo pathway via competitively binding to miR-486-5p	[131]
BCAR4	Up	Breast cancer	YAP enhances its expression; coordinates Hedgehog pathway to promote the transcriptions of HK2 and PFKFB3	[132]
UCA1	Up	Breast cancer	TGF- $\beta$ -Hippo signaling upregulates its expression; activates AKT and STAT3 to promote glycolysis	[134]

(Continued)

**Table 1** (Continued).

LncRNA	Expression	Cancer Type	Functions and Targets	Reference
LINC01420	Up	Pancreatic cancer	Promotes RAS signaling; promotes cancer progression	[137]
LncRNA-ATB	Up	Bladder cancer	Promotes RAS signaling; enhances cell proliferation and invasion	[138]
HI9	Up	Colon cancer	Promotes RAS/MAPK signaling; promotes colon cancer progression	[139]

hydroxylase antisense RNA 1 (DBH-AS1) enhances the glycolytic activity of melanoma cells by GLUT1 and facilitates cell proliferation and metastasis. Further, lncRNA DBH-AS1 suppresses the transcription of miR-223-3p through interacting with its promoter. MiR-223-3p binds directly to the 3' untranslated region (UTR) of GLUT1, leading to decreased GLUT1 expression.<sup>55</sup>

Moreover, the localization of GLUT1 can affect its function. Zhang et al demonstrated that inhibition of translocation of GLUT1 to the cell membrane reduces both glucose uptake and glycolysis in lung cancer cells.<sup>56</sup> LncRNA MACC1 antisense RNA 1 (MACC1-AS1) is overexpressed in gastric cancer tissues and correlated with the malignant behavior of cancer cells.<sup>57</sup> Mechanistically, MACC1-AS1 increases the abundance of GLUT1 on cell membranes by facilitating translocation of GLUT1.<sup>57</sup> MACC1-AS1 thus stimulates glycolysis, in part, through promoting the distribution of GLUT1 to the cell membrane. However, whether lncRNA modulates the distribution of other GLUTs, such as GLUT3 and GLUT4, to affect glucose uptake needs in-depth study.

### LncRNAs and MCTs

MCTs, proton-coupled integral membrane proteins, control lactic acid transport across the plasma membrane. MCTs, particularly MCT1, MCT3 and MCT4, are upregulated in human cancers.<sup>58</sup> Increased MCT expression promotes metastasis, angiogenesis, and metabolic reprogramming by facilitating lactic acid exchange.<sup>58</sup>

Logotheti et al identified a new lncRNA, SLC16A1 antisense RNA 1 (SLC16A1-AS1), transcribed by the antisense strand of the SLC16A1 gene. SLC16A1 encodes MCT1.<sup>59</sup> Further, E2F transcription factor 1 (E2F1) transactivates SLC16A1 and SLC16A1-AS1 due to the shared response promoter. Reciprocally, SLC16A1-AS1 binds with E2F1 and creates a lncRNA–protein complex to co-activate SLC16A1/MCT1. This feed-forward loop leads to enhanced aerobic glycolysis and tumorigenesis in bladder cancer.<sup>59</sup>

## LncRNAs-Mediated Regulatory Mechanisms of Glycolytic Enzymes

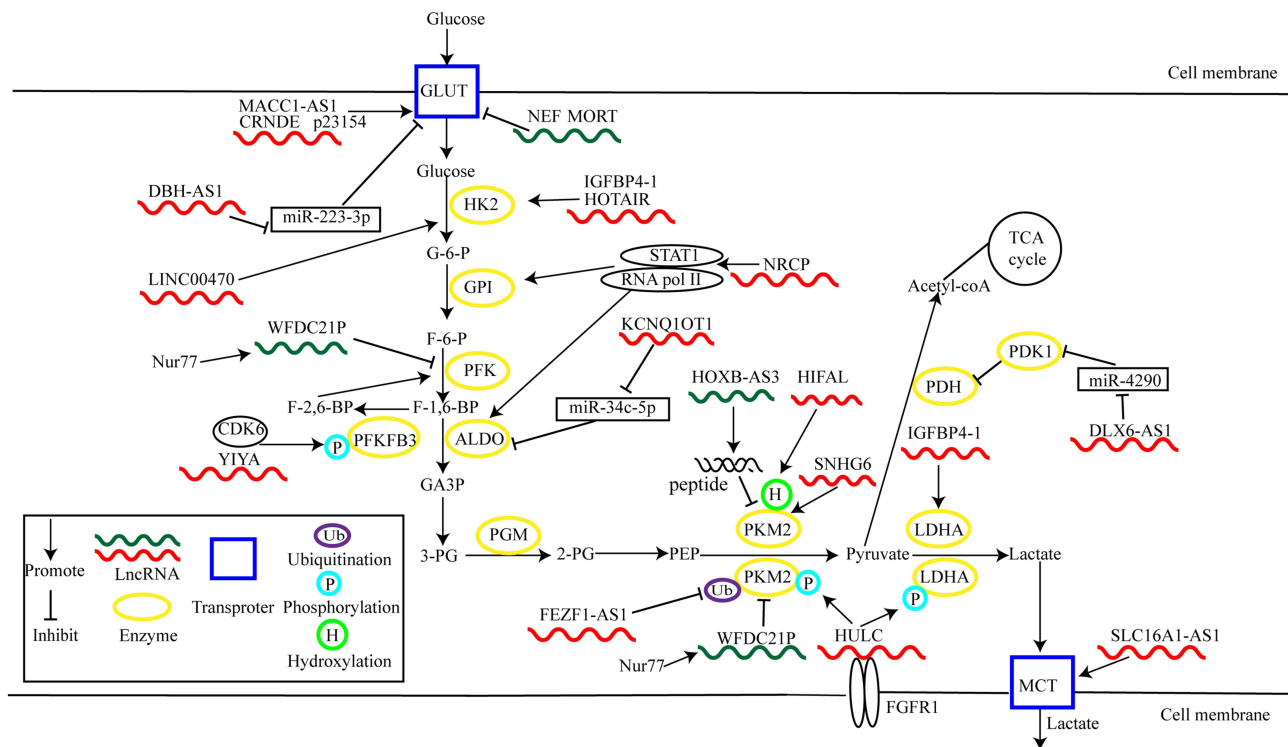
Glycolysis is the process that decomposes glucose into lactate to produce ATP. It contains the steps, catalyzed by corresponding enzymes. During this process, three rate-limiting enzymes work together to convert glucose into pyruvate.<sup>60</sup> Hexokinase (HK) is the first rate-limiting enzyme of the glycolytic metabolism, which converts glucose into glucose-6-phosphate.<sup>61</sup> Phosphofructokinase (PFK) 1 is the second rate-limiting enzyme that catalyzes fructose-6-phosphate (F6P) into fructose-1,6-biphosphate.<sup>62</sup> Pyruvate Kinase (PK) is the last glycolytic rate-limiting enzyme that converts phosphoenolpyruvate (PEP) into pyruvate.<sup>63</sup> Then, lactate dehydrogenase A (LDHA) converts pyruvate into lactate.<sup>64</sup> Moreover, glyceraldehyde 3-phosphate dehydrogenase also plays a vital role in glycolysis. It catalyzes glyceraldehyde 3-phosphate into 1,3-bisphosphoglycerate accompanied by the formation of NADHs.<sup>60</sup>

In addition to affecting GLUT expression or translocation, lncRNAs modulate glycolytic enzymes (Figure 1).

### LncRNAs Directly Regulate Glycolytic Enzymes at Multiple Regulatory Levels

#### Transcriptional Regulation

At the transcriptional level, lncRNAs activate gene expression in aerobic glycolysis. For instance, lncRNA Hox transcript antisense RNA (HOTAIR) is highly expressed in pancreatic adenocarcinoma and associated with poor prognosis. This lncRNA promotes cell proliferation and glycolysis through transcriptional activation of HK2.<sup>65</sup> In ovarian cancer, lncRNA ceruloplasmin (NRCP) promotes aerobic glycolysis and tumor growth. Mechanistically, NRCP, as an intermediate binding partner, promotes an interaction between RNA polymerase II and signal transducer and activator of transcription 1 (STAT1) in the nucleus. This interaction results in increased expression of several glycolytic enzymes, including glucose-6-phosphate isomerase, aldolase A (ALDOA) and ALDOC.<sup>66</sup>



**Figure 1** LncRNAs regulate cancer glycolysis by modulating metabolic enzymes and transporters.

Under glucose starvation, overexpression of lncRNA insulin-like growth factor binding protein 4-1 (IGFBP4-1) upregulates the expression of HK2 and LDHA at the transcriptional level, thus promoting aerobic glycolysis and tumor growth.<sup>67</sup>

### Post-Transcriptional Regulation

At the post-transcriptional level, lncRNAs directly regulate mRNA splicing, protein localization, and act as ceRNAs for miRNAs. In aerobic glycolysis, lncRNAs mediate the post-transcriptional regulation of enzymes, thus affecting their expression and functional diversifications.

### Alternative Splicing

Alternative splicing is essential for proteomic diversity and contributes to spatial and temporal gene expression.<sup>68</sup> Alternative splicing of pyruvate kinase type M (PKM) precursor mRNA by heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) is an important example.<sup>69</sup> PKM exists in two isoforms, PKM1 and PKM2. PKM2-mediated aerobic glycolysis may be advantageous for tumorigenesis, and the ratio of PKM2/PKM1 is commonly upregulated in cancers.<sup>69</sup> Lan et al found that lncRNA small nucleolar RNA host gene (SNHG) 6 is

associated with hnRNPA1-mediated splicing of PKM in colorectal cancer (CRC). SNHG6 directly binds to the precursor mRNA of PKM and induces hnRNPA1 to bind to flanking exon 9. These actions increase the proportion of PKM2/PKM1 and enhance aerobic glycolysis and promote tumor growth. Thus, the role of SNHG6 in carcinogenesis might be exerted by promoting aerobic glycolysis by alternative splicing of PKM.<sup>70</sup>

LncRNAs are often considered as dark matter without encoded peptides.<sup>71</sup> However, one current investigation has reversed this concept. The NR\_033201.2 variant of HOXB cluster antisense RNA 3 (HOXB-AS3) is down-regulated in colon cancer and encodes a small endogenous peptide that acts as a tumor suppressor. This peptide selectively binds to the hnRNPA1 binding domain. This binding targeted sequences adjacent to PKM exon 9 results in downregulation of PKM2 expression. This process reduces lactate production and inhibits glycolytic flux.<sup>72</sup>

### CeRNA

DLX6 Antisense RNA 1 (DLX6-AS1), an upregulated lncRNA in gastric cancer, facilitates aerobic glycolysis and tumor development by acting as a ceRNA for miR-4290. This interaction upregulates pyruvate dehydrogenase kinase 1 (PDK1), a gatekeeper enzyme that inhibits

pyruvate entry into the tricarboxylic acid (TCA) cycle. The enzyme inhibits the formation of acetyl-coA from pyruvate.<sup>73</sup> In osteosarcoma, lncRNA potassium voltage-gated channel subfamily Q member 1 opposite strand 1 (KCNQ1OT1) can sponge miR-34c-5p to enhance expression of ALDOA, thus facilitating aerobic glycolysis and tumor growth.<sup>74</sup>

### Localization

LncRNAs modulate glycolytic enzyme activity by affecting their localization. Guan et al found that nuclear receptor subfamily four group A member 1 (Nur77) activates transcription of lncRNA WAP four-disulfide core domain 21 pseudogene (WFDC21P). Transcription of the lncRNA attenuates the Warburg effect and hepatocarcinogenesis. Mechanistically, WFDC21P inhibits tetramer formation of phosphofructokinase, platelet type (PFKP) and inhibits its catalytic activity. It also blocks nuclear localization of PKM2, thus suppressing its transcriptional activation of oncogenic factors, including c-Myc and hypoxia-inducible factor (HIF)-1 $\alpha$ .<sup>75,76</sup> Thus, the Nur77/WFDC21P axis may be a promising therapeutic target for HCC, though its regulation remains elusive.

### Post-Translational Regulation

LncRNAs mediate post-translational regulation of several enzymes in aerobic glycolysis, thus influencing the formation and degradation of proteins. The main post-transcriptional modifications are phosphorylation and ubiquitination. For example, lncRNA highly up-regulated in liver cancer (HULC) directly binds to LDHA and PKM2 and enhances their binding with fibroblast growth factor receptor type 1 (FGFR1). These interactions result in elevated phosphorylation of the two enzymes, thus promoting glycolysis and cell proliferation.<sup>77</sup> Additionally, lncRNA LINC00538 (YIYA) facilitates glycolytic flux and breast cancer growth through regulating cyclin-dependent kinase 6 (CDK6) dependent phosphorylation of fructose biphosphatase PFK2 (PFKFB3).<sup>78</sup> This enzyme converts F-6-P into fructose-2,6-bisphosphate (F-2,6-BP).<sup>79</sup> Fez family zinc finger protein 1 antisense ribonucleic acid 1 (FEZF1-AS1), an upregulated lncRNA in CRC, accelerates metastasis and proliferation of cancer cells. FEZF1-AS1 increases the stability of PKM2 protein through inhibiting ubiquitin-mediated degradation. These actions lead to enhanced expression of PKM2 in the cytoplasm and nucleus and increased aerobic glycolysis.<sup>80</sup>

Liu et al reported that LINC00470 directly binds with a ternary complex composed of RNA-binding protein

fused in sarcoma (FUS) and V-akt murine thymoma viral oncogene homolog (AKT). This binding leads to AKT phosphorylation. Elevated AKT phosphorylation prevents HK1 from ubiquitinate-mediated degradation, thus enhancing aerobic glycolysis and carcinogenesis.<sup>81</sup>

Interestingly, the post-translational modification of PKM2 can trigger Warburg effect. For example, HIF-1 $\alpha$  antisense lncRNA (HIFAL) recruits proline hydroxylase domain (PHD) 3 to PKM2 and promotes prolyl hydroxylation at proline 408. Hydroxylated PKM2 drives nuclear translocation of hydroxyl-PKM2/PHD3 complex through binding with heterogeneous nuclear ribonucleoprotein F (hnRNP). This process promotes HIF-1 $\alpha$  transactivation, resulting in enhanced expression of LDHA, PDK1, GLUT1, and HK2. Further, activated HIF-1 $\alpha$  potentiates HIFAL transcription, inducing the positive HIF-1 $\alpha$ - HIFAL- HIF-1 $\alpha$  regulation and promoting aerobic glycolysis and tumor growth.<sup>82</sup>

In conclusion, lncRNA may control the function of glycolytic enzymes at the post-translational level through adding or removing functional groups. These changes regulate glycolytic flux and cancer development.

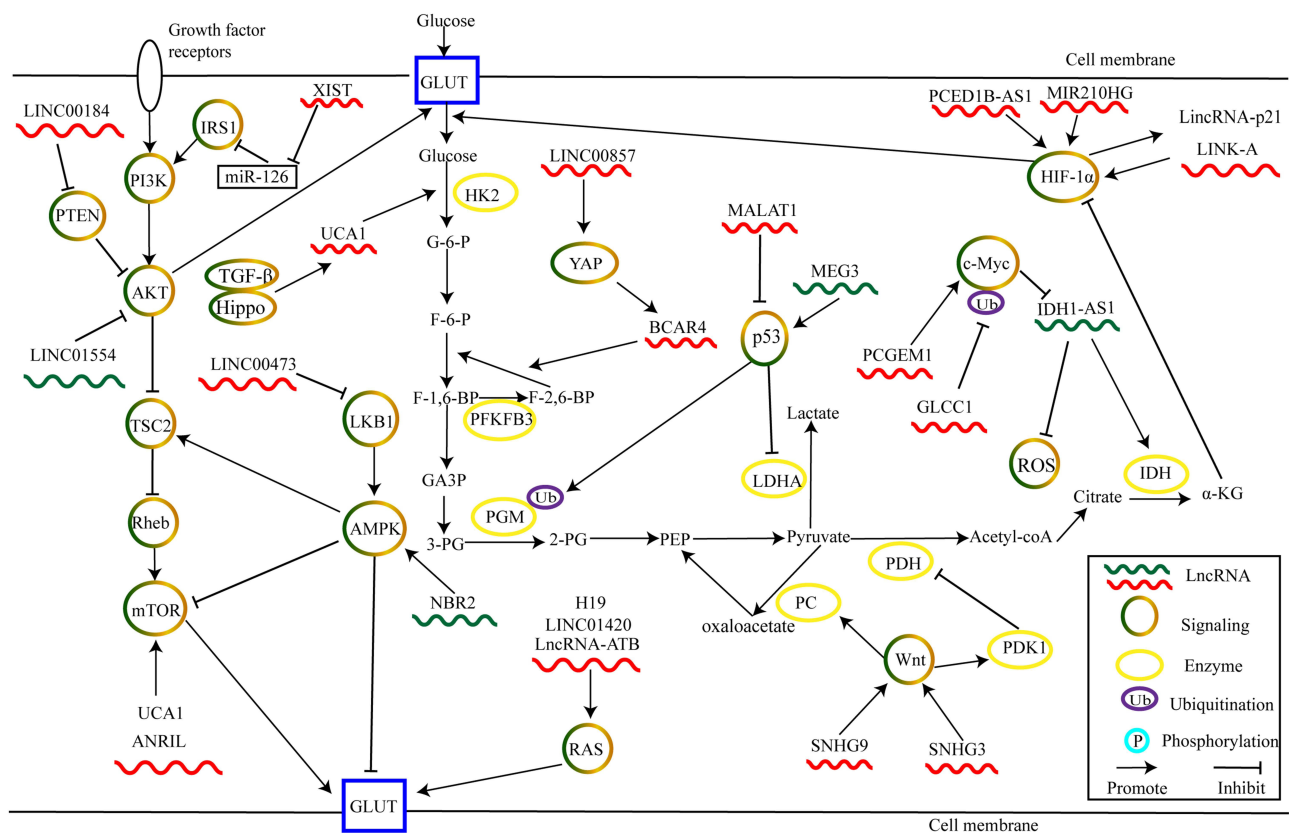
### LncRNAs Regulate Glycolytic Enzymes Through Signaling Pathways

An interaction between dysregulated lncRNAs and signal transduction pathways significantly contributes to alteration of cancer glycolysis, thereby promoting or inhibiting carcinogenesis and cancer progression (Figure 2).

#### HIF Signaling

The aerobic glycolysis is closely associated with hypoxic tumor microenvironment.<sup>18</sup> HIF serves as an important transcription factor expressed by malignant cell adapted to anoxic environments.<sup>83</sup> Activating HIF-1 $\alpha$  enhances a glycolytic phenotype through promoting transcription of GLUTs or glycolysis-related enzymes.<sup>84</sup> LncRNAs play critical regulatory roles in HIF signaling. LncRNA PCED1B antisense RNA 1 (PCED1B-AS1) supports the translation of HIF-1 $\alpha$  mRNA by directly binding to its 5'-UTR, leading to enhanced HIF-1 $\alpha$  expression. Increased HIF-1 $\alpha$  expression potentiates aerobic glycolysis and carcinogenesis in glioblastoma.<sup>85</sup> In triple-negative breast cancer (TNBC), overexpression of lncRNA miR210 host gene (MIR210HG) increases HIF-1 $\alpha$  protein levels and upregulates the expression of glycolysis target genes such as GLUT1, PKM2, LDHA. These alterations enhance glucose consumption and tumor growth.<sup>86</sup>





**Figure 2** LncRNAs regulate cancer glycolysis by modulating metabolic pathways.

Under normoxia, the PHD-dependent hydroxylation of HIF-1 $\alpha$  at Proline 402 or Proline 564 leads to destabilization of HIF-1 $\alpha$  via the von Hippel-Lindau protein (VHL)-mediated ubiquitination process. Ubiquitination leads to rapid degradation in the proteasome pathway.<sup>87</sup> Thus, inhibition of hydroxylation and subsequent ubiquitin-mediated degradation of HIF-1 $\alpha$  is a critical aspect of regulating its function in aerobic glycolysis. For example, one study showed that accumulation of HIF-1 $\alpha$  leads to enhanced transcription of long intergenic noncoding RNA (lincRNA)-p21 under hypoxic conditions.<sup>88</sup> Moreover, overexpressed lincRNA-p21 competitively binds with HIF-1 $\alpha$  to disrupt the interaction between HIF-1 $\alpha$  and VHL. Thus, HIF-1 $\alpha$  is stabilized by inhibition of ubiquitin-mediated degradation. This reciprocal regulation ensures a high level of active HIF-1 $\alpha$  during hypoxia. In turn, increased HIF-1 $\alpha$  expression leads to activation of GLUT1 and LDHA, which facilitates the Warburg effect.<sup>88</sup> Lin and colleagues revealed that a cytoplasmic lincRNA, long intergenic noncoding RNA for kinase activation (LINK-A), promotes reprogramming of glucose metabolism and tumorigenesis in TNBC.<sup>89</sup> LINK-A recruited

breast tumor kinase (BRK) binds to EGFR- heterodimer and transmembrane glycoprotein NMB (GPNMB) complex and subsequently activates BRK kinase. Activated BRK kinase phosphorylates HIF-1 $\alpha$  at tyrosine 565. This phosphorylation results in inhibition of HIF-1 $\alpha$  hydroxylation at proline 564 and prevents its subsequent degradation. Moreover, LINK-A also recruits leucine-rich repeat kinase 2 (LRRK2) to mediate phosphorylation of HIF-1 $\alpha$  at Ser797, thereby activating its target genes.<sup>89</sup>

### c-Myc Signaling

The MYC gene family is a canonical oncogene that is widely downregulated in tumors.<sup>90</sup> The MYC oncogene encodes c-Myc, a transcription factor that promotes glycolysis through activating glycolytic enzymes.<sup>91</sup> For instance, lincRNA prostate cancer gene expression marker 1 (PCGEM1) is overexpressed in prostate cancer and is advantageous for cancer cell growth via metabolic reprogramming. PCGEM1 promotes transcriptional activation of metabolic genes through enhancing histone H3 and H4 acetylation of c-Myc. Moreover, silencing PCGEM1 inhibits the expression of several genes and attenuates

glycolysis. Thus, PCGEM1 plays a critical role in prostate cancer metabolism.<sup>92</sup> In CRC, glycolysis-associated lncRNA of colorectal cancer (GLCC1) is highly expressed during energy stress and is associated with poor prognosis. Mechanistically, GLCC1 strengthens the interaction between heat shock protein 90 (HSP90) and ubiquitin-specific protease 22 (USP22), an important deubiquitinating enzyme. Consequently, c-Myc, the target of HSP90, is stabilized by abolishing proteasome-mediated degradation. c-Myc can then support transcriptional activation of LDHA and promote glycolysis and cell proliferation.<sup>93</sup>

Existing evidence has revealed that ROS plays a vital role in aerobic glycolysis.<sup>94</sup> Moreover, Xiang et al found that c-Myc is the regulator of ROS. c-Myc transcriptionally represses lncRNA isocitrate dehydrogenase 1 (IDH1) antisense RNA1 (IDH1-AS1). IDH1-AS1 increases the activity of IDH1 by potentiating its dimerization. This process enhances the production of  $\alpha$ -ketoglutarate ( $\alpha$ -KG) and reduces ROS under normoxia.<sup>95</sup>  $\alpha$ -KG, a component of the TCA cycle, is involved in the degradation of HIF-1 $\alpha$ .<sup>96</sup> Thus, lncRNA IDH1-AS1 regulated by c-Myc destabilizes HIF-1 $\alpha$  through activating the IDH1- $\alpha$ KG/ROS-HIF1 $\alpha$  cascade, leading to inhibition of Warburg effect.<sup>95</sup>

### PI3K Signaling

Growth factors stimulate phosphoinositide 3-kinase (PI3K) and activate the AKT/mechanistic target of rapamycin (mTOR) axis. This axis plays an important role in numerous physiological processes, such as tumorigenesis and metabolic reprogramming.<sup>97,98</sup> Notably, AKT activates mTORC1 by inhibiting tuberous sclerosis complex 2 (TSC2) activity. This inhibition leads to repression of Ras homolog enriched in brain guanosine triphosphatase (Rheb GTPase).<sup>99</sup> In this process, phosphatase and tensin homolog on chromosome 10 (PTEN) negatively controls PI3K signaling by inactivating AKT.<sup>100</sup> For example, overexpression of LINC00184 recruits DNA methyltransferase 1 (DNMT1) to the promoter of PTEN, thus inhibiting its expression. Decreased PTEN removes its repression of the PI3K/AKT cascade and leads to enhanced glycolysis in esophageal cancer.<sup>101</sup>

Additionally, AKT activates mTOR, which in turn upregulates GLUTs or glycolytic enzymes. Antisense non-coding RNA in the INK4 locus (ANRIL) activates AKT/mTOR signaling to upregulate GLUT-1, resulting in enhanced glycolysis in nasopharyngeal carcinoma.<sup>102</sup> Li et al reported that urothelial cancer-associated 1 (UCA1)

activates mTOR to upregulate HK2 via both activating STAT3 and inhibiting miR-143, thereby uncovering a novel metabolic cascade in bladder cancer.<sup>103</sup> Zheng et al revealed that LINC01554 inactivates AKT/mTOR signaling pathway to abolish tumorigenicity and glycolysis in HCC.<sup>104</sup>

Insulin receptor substrate (IRS) is a cytoplasmic adaptor protein that amplifies the PI3K signal and plays a critical role in cancer metabolism.<sup>105</sup> Cheng et al demonstrated that lncRNA X-inactive specific transcript (XIST) is highly expressed in glioblastoma and directly sponges miR-126. This activity promotes glycolysis via the IRS1/PI3K/Akt/GLUT cascade.<sup>106</sup> Thus, IRS1/PI3K/AKT may provide one mechanism for metabolism reprogramming. The complex combinatorial possibilities of the IRS/PI3K/AKT pathway may affect cancer metabolic remodeling through multiple dimensions.<sup>107</sup> More studies are needed to explore this linkage.

### LKB1/AMP-Activated Protein Kinase (AMPK) Signaling

AMPK is an energy sensor. Cancer cells typically down-regulate AMPK to evade confining influences on proliferation and develop their glycolytic phenotype.<sup>108</sup> Activated AMPK phosphorylates the TSC2 complex, inhibiting the activity of Rheb. Rheb inhibition results in the inactivation of mTOR.<sup>109</sup> Under energy stress, activated TSC2 mediated by AMPK reduces cell apoptosis.<sup>110</sup>

Liver kinase B1 (LKB1), a critical tumor suppressor, modulates cell growth and metabolism through regulating mTOR activity.<sup>111</sup> As a primary upstream modulator of AMPK, LKB1 activates AMPK in response to low intracellular levels of ATP. Low ATP levels inhibit cell proliferation.<sup>112</sup> Knockdown of LKB1 facilitates tumor growth, with elevated uptake of glucose, upregulated ATP production, and synthesis of macromolecules.<sup>113</sup> Zeng et al revealed that LKB1 inhibits human papillomavirus (HPV)-induced glycolysis. Loss of LKB1 facilitates HPV-stimulated tumor metastasis through upregulating the expression of HK2.<sup>114</sup> LKB1 deficiency thus promotes glycolysis and tumorigenesis.

Nuclear lncRNA LINC00473 interacts with non-POU domain-containing octamer-binding protein (NONO), a regulator of cancer glycolytic metabolism.<sup>115,116</sup> LINC00473 is induced by LKB1 loss and promotes lung tumor growth.<sup>115</sup> Under energy stress, the LKB1/AMPK pathway activates the transcription of lncRNA neighbor of BRCA1 gene 2 (NBR2), which potentiates AMPK activation. Depletion of NBR2 counteracts glucose-starvation-

induced AMPK activation, leading to alterations in the apoptosis/autophagy responsive ratio and enhanced breast cancer development. These findings suggest the modulation of the NBR2/AMPK feed-forward loop mechanism.<sup>117</sup> Additionally, NBR2 attenuates thyroid cancer epithelial-mesenchymal transition and GLUT-1 expression by potentiating AMPK activation.<sup>118</sup> Therefore, interactions between lncRNAs and LKB1/AMPK signaling pathway play a critical role in cancer glycolysis.

### P53 Signaling

p53, a well-known tumor suppressor, is deregulated in many cancers.<sup>119</sup> Recently, several studies have revealed that p53 is crucial in cancer glycolysis. The cellular absence of p53 increases glycolysis.<sup>119</sup> p53 directly inhibits the transcription of GLUT1 and GLUT4 to decrease glucose uptake.<sup>120</sup> p53 also participates in glucose metabolism via modulating expression of multiple glycolytic enzymes. Activated p53 enhances ubiquitinate-mediated degradation of phosphoglycerate mutase (PGM), which inhibits the production of pyruvate.<sup>121</sup> p53 also controls LDHA transcriptional activity through an interaction with the LDHA promoter region. This action attenuates glycolysis in breast cancer.<sup>122</sup>

lncRNAs interact with p53 signaling directly or indirectly. In HepG2 cells, lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) enhances deacetylases sirtuin 1 (SIRT1)- deacetylated-p53 and inhibits the transcription of its target genes. These actions promote cell growth.<sup>123</sup> Overexpression of maternally expressed gene 3 (MEG3) increases p53 expression and activates its target genes.<sup>124</sup> MEG3 promotes p53-mediated transactivation, thereby inhibiting breast cancer development.<sup>125</sup> Accordingly, MALAT1 and MEG3 are critical to the p53 pathway, but detailed mechanisms need further investigation.

Overall, the role of p53 pathway in cancer development is partially manifested in inhibition of glucose metabolic reprogramming, and lncRNAs may play a crucial role in these processes.

### Wnt Signaling

Lee et al demonstrated that wingless (Wnt) facilitates glycolysis via upregulating pyruvate carboxylase (PC). This enzyme is critical for the conversion of pyruvate to oxaloacetate.<sup>126</sup> Pate et al then reported that inhibition of the Wnt/ $\beta$ -catenin pathway leads to reduced glycolysis in colon cancer cells. Mechanistically, Wnt regulated

glycolytic metabolism, in part, through controlling PDK1.<sup>127</sup> These findings reveal that Wnt/ $\beta$ -catenin signaling pathway promotes aerobic glycolysis through regulating PC and PDK1, enzymes that switch metabolic energy production from oxidative phosphorylation to aerobic glycolysis.

lncRNAs are implicated in glycolytic metabolism and cancer progression via the Wnt/ $\beta$ -catenin pathway. For example, Zhang et al showed that lncRNA SNHG9 is involved in aerobic glycolysis of glioblastoma. They suggested that overexpression of SNHG9 promotes glycolytic metabolism and cell growth by downregulating miR-199a-5p and upregulating Wnt2.<sup>128</sup> In laryngeal squamous cell carcinoma, knockdown of SNHG3 inhibits glycolysis and tumor growth by eliminating the Wnt pathway via modulating miR-340-5p/yes-associated protein 1 (YAP1) axis.<sup>129</sup> However, whether lncRNAs-mediated Wnt/glycolysis signaling correlates with alterations in PC and PDK1 awaits further investigation.

### Other Signaling

The Hippo pathway plays an important role in organ development and tissue homeostasis by suppressing YAP/PDZ-binding motif (TAZ) transcription co-activators. The deregulated Hippo pathway usually causes tumorigenesis in model organisms.<sup>130</sup> Currently, several studies have revealed that Hippo pathway is a key regulator of cancer glycolysis. For example, LINC00857 promotes ovarian cancer glycolysis through upregulating YAP1.<sup>131</sup> Additionally, YAP enhances the expression of lncRNA Breast Cancer Antiestrogen Resistance 4 (BCAR4), which coordinates the Hedgehog pathway to upregulate HK2 and PFKFB3 in breast cancer.<sup>132</sup>

Transforming growth factor beta (TGF- $\beta$ ) pathway is considered as a pro-metastatic signaling by inducing EMT.<sup>133</sup> However, TGF- $\beta$  also cooperates with Hippo signaling in cancer glycolysis. Mota et al reported that loss of tumor suppressor Merlin results in the loss of small mothers against decapentaplegic 7, which activates TGF- $\beta$  and enables the co-operative engagement of TGF- $\beta$ -Hippo signaling. This process upregulates lncRNA UCA1 that enhances the expression of HK2, leading to increased aerobic glycolysis in breast cancer cells.<sup>134</sup>

Kirsten rat sarcoma viral oncogene homolog (KRAS), an important member of RAS family, is mutated in various cancers.<sup>135</sup> Mutated KRAS has been reported to promote aerobic glycolysis through upregulating GLUT1 and glycolytic enzymes.<sup>136</sup> LINC01420 promotes pancreatic

cancer progression through upregulating KRAS.<sup>137</sup> Long noncoding RNA activated by TGF- $\beta$  (lncRNA-ATB) has been reported to enhance cell proliferation and invasion of bladder cancer through miR-126/KRAS axis.<sup>138</sup> Moreover, lncRNA H19 promotes colon cancer progression by activating RAS/mitogen-activated protein kinase (MAPK) signaling pathway.<sup>139</sup> In conclusion, LINC01420, lncRNA-ATB, H19 may be critical regulators of RAS. More studies are needed to understand their functions in aerobic glycolysis.

## Deregulated Mechanisms of LncRNAs in Cancer Glycolysis Epigenetic Regulation

LINC00261 is downregulated in pancreatic cancer cell lines and overexpressed LINC00261 inhibits glycolysis and proliferation of pancreatic cancer cells. Mechanistically, LINC00261 is downregulated by enhancer of zeste homolog 2 (EZH2)-mediated histone H3 lysine 27 trimethylation and high methylated levels in the promoter region. This finding reveals novel epigenetic regulatory mechanisms of LINC00261 in pancreatic cancer glycolysis and provides a promising target for pancreatic cancer targeted therapy.<sup>140</sup>

## Transcriptional Regulation

Transcription factor AP2alpha (TFAP2A) plays an essential role in regulating cell proliferation and differentiation.<sup>141</sup> Moreover, Zhang et al found that TFAP2A directly binds to the promoter region of lncRNA SNHG16 and activates its transcription. Activated SNHG16 promotes the proliferation and glycolysis of endometrial carcinoma.<sup>142</sup> Moreover, lncRNAs can be regulated by c-Myc. In NSCLC, c-Myc activates LINC01123 to promote aerobic glycolysis.<sup>143</sup> On the contrary, c-Myc transcriptionally represses IDH1-AS1.<sup>95</sup> Additionally, lncRNAs may also be transcriptional targets of p53. LncRNA actin gamma 1 pseudogene (AGPG) stabilizes PFKFB3 by inhibiting its ubiquitination and subsequent degradation. Upregulated PFKFB3 stimulates glycolytic flux and cell proliferation. Moreover, AGPG is repressed by p53, which indicates a p53-AGPG-PFKFB3 axis may be a promising target for cancer treatment.<sup>144</sup> Liao et al reported that lncRNA EPB41L4A antisense RNA 1 (EPB41L4A-AS1), a p53 inducible lncRNA, is downregulated in multiple cancers. Knockdown of EPB41L4A-AS1 enhances the localization of histone deacetylase 2 (HDAC2) in the nucleoplasm, promotes HDAC2 occupation on the

VHL promoter region, stabilizes HIF-1 $\alpha$ , and thus promotes glycolysis.<sup>145</sup> This finding links two critical glycolytic pathways, reflecting cancer metabolism complexity and the need for further study.

It has been reported that *Fusobacterium nucleatum* (*F. nucleatum*) is highly abundant in CRC tissues and correlated with the poor prognosis in patients with CRC.<sup>146</sup> But the detail molecular mechanism is unknown. Hong et al found that *F. nucleatum* supports carcinogenesis by promoting CRC cell glycolysis. Mechanistically, *F. nucleatum* activates lncRNA enolase1-intronic transcript 1 (ENO1-IT1) transcription through recruiting transcription factor specificity protein 1 (SP1) to the promoter region of ENO1-IT1. Upregulated ENO1-IT1 activates the target genes including ENO1, resulting in elevated glycolysis and enhanced tumor growth.<sup>147</sup>

HIF-1 $\alpha$  induces upregulation of lncRNA AC020978 in NSCLC. Elevated AC020978 stabilizes PKM2 by protecting it from degradation. Stabilized PKM2 augments HIF-1 $\alpha$  transcriptional activity. This positive AC020978/PKM2/HIF-1 $\alpha$  loop activates Warburg effect.<sup>148</sup> Moreover, other lncRNAs such as HIFAL and linc-p21 form positive feedback loops as well.<sup>82,88</sup> On the one hand, hypoxia induces the upregulation of lncRNAs. On the other hand, lncRNAs can promote the transcriptional activity of HIF-1 $\alpha$ , thus facilitating the glycolysis.

Overall, during aerobic glycolysis, lncRNAs expression can be regulated by epigenetic mechanisms. Additionally, several transcriptional factors regulate lncRNAs expression as well (Table 2 and Figure 3).

## MiRNAs and CircRNAs in Cancer Glycolysis

MiRNAs and circRNAs are important ncRNAs in tumorigenesis. Moreover, recent studies have shown the involvement of miRNAs and circRNAs in cancer glycolysis.<sup>149</sup> Several miRNAs have been shown to regulate the expression of GLUT1 and GLUT3. For example, miR-148b downregulates GLUT1, thus impeding gastric cancer glycolysis.<sup>150</sup> Moreover, miR-10a enhances cancer cell glycolysis and proliferation in OSCC via upregulating GLUT1.<sup>151</sup> In bladder cancer, miR-195-5p inhibits glycolysis and cell proliferation by downregulating GLUT3.<sup>152</sup> Additionally, miRNAs also regulate several glycolytic enzymes. In NSCLC, miR-214 upregulates HK2 and PKM2 through PTEN/Akt/mTOR signaling pathway.<sup>153</sup> Wang et al reported that LDHA is targeted by several miRNAs including miR-

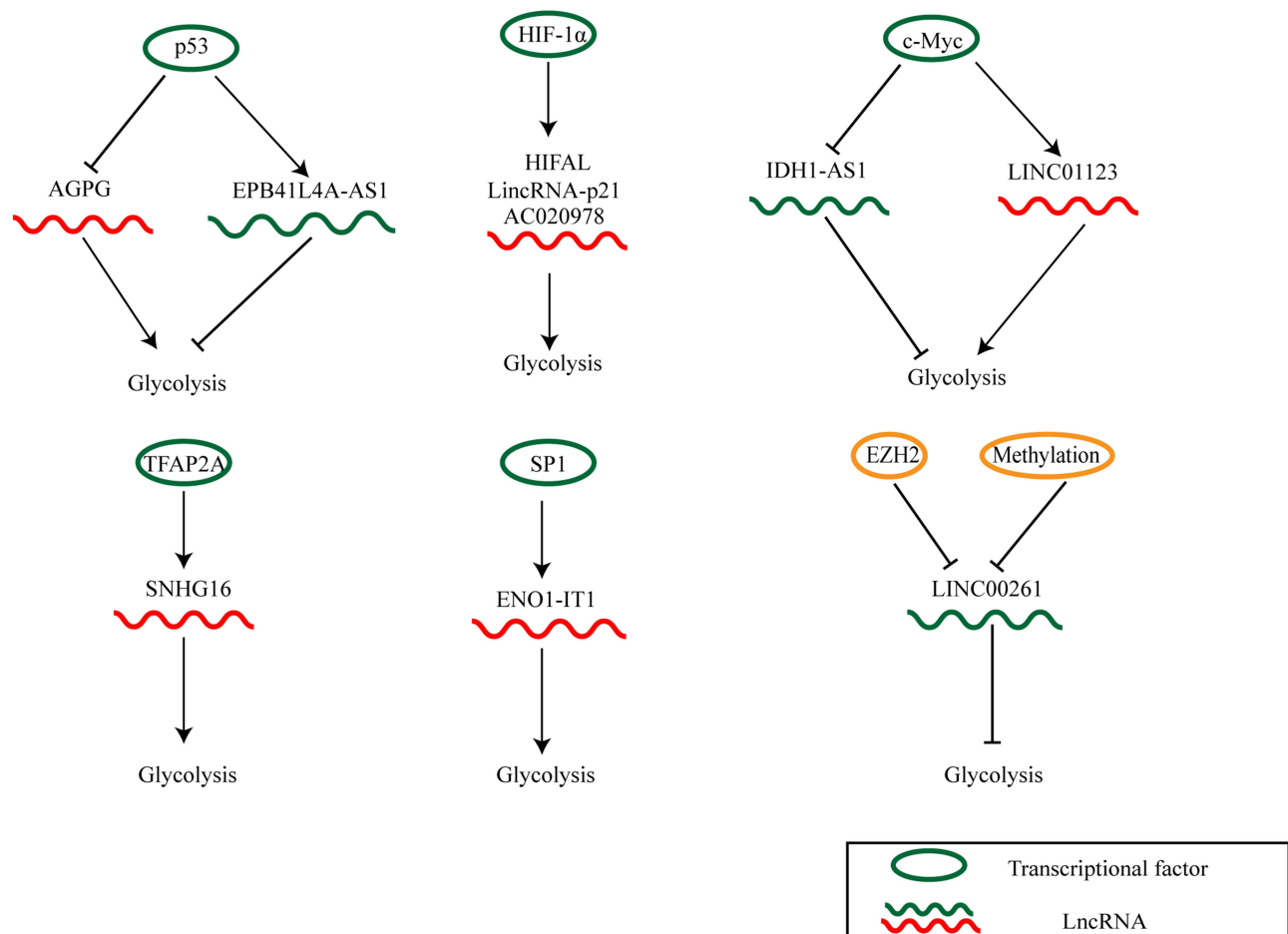
**Table 2** The Deregulated Mechanisms of lncRNAs in Aerobic Glycolysis

LncRNA	Expression	Regulatory Molecules	Regulatory Mechanisms	Reference
LINC00261	Down	EZH2	EZH2 and DNA methylation inhibit its expression	[140]
SNHG16	Up	TFAP2A	TFAP2A activates its transcription	[142]
LINC01123	Up	c-Myc	c-Myc activates its transcription	[143]
IDH1-AS1	Down	c-Myc	c-Myc inhibits its transcription	[95]
AGPG	Up	p53	p53 inhibits transcription	[144]
EPB41L4A-AS1	Down	p53	p53 activates its transcription	[145]
ENO1-IT1	Up	SP1	F. nucleatum recruit SP1 to activate its transcription	[147]
AC020978	Up	HIF-1 $\alpha$	HIF-1 $\alpha$ activates its transcription	[148]
HIFAL	Up	HIF-1 $\alpha$	HIF-1 $\alpha$ activates its transcription	[82]
linc-p21	Up	HIF-1 $\alpha$	HIF-1 $\alpha$ activates its transcription	[88]

34a, miR-34c, miR-369-3p, miR-374a, and miR-4524a/b, thereby altering glycolysis in CRC.<sup>154</sup>

Mounting evidence has shown that circRNAs regulate glycolysis through multiple mechanisms: (i) circRNAs act as ceRNAs for miRNAs. (ii) circRNAs regulate gene transcription. (iii) circRNAs encode peptides. For

example, circRNA MAT2B facilitates HCC glycolysis via miR-338-3p/PKM2 axis.<sup>155</sup> CircMDM2 accelerates the glycolysis of OSCC through targeting miR-532-3p/HK2 axis.<sup>156</sup> CircFNDC3B-218aa, a novel peptide encoded by circFNDC3B, can inhibit glucose uptake, lactate production and cell invasion in colon cancer.<sup>157</sup>



**Figure 3** The deregulated mechanisms of lncRNAs in cancer glycolysis.

Obviously, miRNAs, circRNAs, and lncRNAs are all important regulators in cancer glycolysis. Therefore, understanding their regulatory mechanisms in aerobic glycolysis may provide efficient strategies for cancer treatment.

## Perspectives: The Potential Therapeutic Role of LncRNAs

Cancer is the primary cause of human mortality, and resistance of tumors to therapeutic interventions significantly impedes cancer treatment. More efficient strategies to evade resistance and successfully treat cancer have been sought for decades. Liu et al noted the role of LINC00518 in radio-resistance of cutaneous malignant melanoma (CMM) from the perspective of aerobic glycolysis and proposed LINC00518 as a promising target for improving the treatment outcomes of patients receiving radiotherapy. Knockdown of LINC00518 inhibits glycolysis through downregulating LDHA protein levels via the miR-33a-3p/HIF-1 $\alpha$  axis. This inhibition enhances the radiosensitivity of CMM cells. Moreover, treatment with an inhibitor of glycolysis, 2-deoxy-D-glucose, reverses the positive effect of overexpression of LINC00518 on LDHA and HIF-1 $\alpha$  expression and radio-resistance in CMM cells. The discovery of the LINC00518/miR-33a-3p/HIF-1 $\alpha$ /LDHA/axis in the radiotherapy of CMM identifies glycolysis as an efficient target to increase the therapeutic efficiency of radiotherapy.<sup>15</sup> Moreover, targeting the UCA1/HK2/glycolysis pathway can also be a method to increase the radiosensitivity of cervical cancer.<sup>158</sup>

Aberrant energy metabolism is a hallmark of cancer, and biguanides are potential anticancer drugs for their abilities to regulate glycolysis.<sup>159</sup> Phenformin is a kind of biguanide used as a chemotherapeutic agent because it impedes cancer development.<sup>160</sup> Liu et al found that lncRNA NBR2 is a likely regulator in cancer cells for the adaptive response under energy stress. Enhanced NBR2 expression inhibits apoptosis induced by phenformin and increases glucose uptake through elevating GLUT1 expression. Upregulation of NBR2 also promotes tumor growth.<sup>161</sup> Several lncRNAs, such as SNHG7,<sup>16</sup> HOTAIR,<sup>162</sup> XIST<sup>163</sup> are also involved in resistance to cisplatin, temozolomide and 5-fluorouracil via altering glycolysis in gastric cancer, glioblastoma and CRC, respectively. Interestingly, Fu et al reported that lncRNA plasmacytoma variant translocation 1 (PVT1) maintains Myc expression in Sjögren's syndrome. This expression regulates proliferation and immune effects of CD4<sup>+</sup> T cells by controlling glycolytic metabolism.<sup>164</sup>

Investigating the role of the PVT1-T cell glycolysis axis in tumor models may provide a novel insight for improving T cell-based immunotherapy.

The important role of lncRNAs-mediated glucose metabolic reprogramming in cancer adjuvant therapy, as discussed above, makes them promising targets for treating cancers. Several studies have revealed that siRNA, antisense oligonucleotides (ASOs) and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) may be promising methods of targeting lncRNAs.<sup>165</sup> However, the application of lncRNAs-based targeted treatment faces several challenges. For example, both the gene network triggering aerobic glycolysis and the intricate molecular mechanisms linking metabolic reprogramming with therapeutic resistance remain to be fully investigated. Only a small number of lncRNAs are clearly understood. Moreover, several studies have revealed that the same lncRNA may play diametrically opposite functional roles in different types of cancers. For example, HOXB-AS3 plays an oncogenic role in lung cancer, acute myeloid leukemia (AML), hepatoma, and epithelial ovarian cancer (EOC).<sup>166–169</sup> Xu et al reported that HOXB-AS3 promotes EOC glycolysis by altering LDHA expression.<sup>166</sup> However, Huang et al reported that HOXB-AS3 is downregulated in colon cancer and encodes a peptide to inhibit glycolysis.<sup>72</sup> Papaioannou et al proposed that the HOXB-AS3 transcript variant in AML cells presents limited overlap with its variant that is downregulated in colon cancer cells. HOXB-AS3, which promotes cell growth in AML, shows high concentrations in the nucleus and a low association with polysomal fractions.<sup>168</sup> It may be a reasonable explanation for the differential functions of HOXB-AS3 in different cancers. Additionally, NF-kappa B interacting long noncoding RNA (NKILA) exerts anti-tumor activity in various cancers,<sup>170</sup> but stimulates aerobic glycolysis and angiogenesis in gliomas.<sup>171</sup> This activity awaits further investigation.

Further, inhibiting oncogenic lncRNAs by siRNAs requires an engineered delivering system to maintain serum stability, prevent immune destruction, and act specifically on tumor cells. Poor membrane permeability of ASOs<sup>172</sup> makes ASOs-based therapy difficult to employ for nuclear lncRNA as a target. Further technological advancement is needed to address this problem. Also, CRISPR/Cas9 system that contains a single guide RNA (sgRNA) and a Cas9 enzyme is now a prevalent approach for targeting lncRNAs. Potent off-target actions are the

major obstacles for the clinical application of CRISPR/Cas9. Modifying Cas9 or sgRNA<sup>173</sup> and sgRNA truncation<sup>174,175</sup> are strategies for reducing these off-target effects. Further research is needed to identify stable and efficient means to overcome off-target effects and allow clinical application of CRISPR/Cas9. Finally, lncRNAs display notable high tissue specificity. LncRNAs expression may vary even within distinct tumor cells and in different individuals due to tumor heterogeneity. Such variability may interject uncertainty into evaluation and verification at the preclinical stage. Developing advanced sequencing and analytical techniques can ensure precise screening of differentially expressed lncRNAs in cancers. Such study will improve understanding of underlying molecular mechanisms in cancer glycolysis and promote the application of lncRNA-based clinical therapy.

## Conclusion

Cancer cells exhibit distinct metabolic characteristics that employ glycolysis to provide energy and intermediary metabolites. This specific metabolic phenomenon is advantageous for cancer cell survival. We highlight regulatory mechanisms of lncRNAs in cancer glycolysis in this review. LncRNAs interact with metabolic enzymes or transporters involved in glycolysis and significantly influence glycolytic metabolism and cancer progression. Additionally, deregulated signaling pathways are vital for cancer glycolysis. LncRNAs, the crucial regulators of glycolysis, are the target of substantial researches into possible therapeutic targets for cancer treatment. More comprehensive investigations are required to explore underlying mechanisms by which lncRNAs regulate aerobic glycolysis. Understanding these mechanisms will promote the development of lncRNA-based strategies to control aberrant metabolic reprogramming and cancer development. Ultimately, such effort will lead to successful clinical application.

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This article does not contain any studies with human participants/animals performed by any of the authors.

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## Disclosure

All the authors declare that they have no conflicts of interest.

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