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REVIEW

Circular RNAs Regulate Glucose Metabolism in Cancer Cells

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Abstract: Circular RNAs (circRNAs) were originally thought to result from RNA splicing errors. However, it has been shown that circRNAs can regulate cancer onset and progression in various ways. They can regulate cancer cell proliferation, differentiation, invasion, and metastasis. Moreover, they modulate glucose metabolism in cancer cells through different mechanisms such as directly regulating glycolytic enzymes and glucose transporter (GLUT) or indirectly regulating signal transduction pathways. In this review, we elucidate on the role of circRNAs in regulating glucose metabolism in cancer cells, which partly explains the pathogenesis of malignant tumors, and provides new therapeutic targets or new diagnostic and prognostic markers for human cancers.

Keywords: circRNAs, glucose metabolism, Warburg effect, signaling pathway, targeted therapy

Background

Glucose metabolism is one of the most basic life properties. Under normoxia, most differentiated cells convert glucose into carbon dioxide and acetyl coenzyme A through oxidative phosphorylation to maintain energy metabolism. Besides, under anoxic conditions, glucose is directly reduced to lactic acid through glycolysis. In the 1920s, Otto Heinrich Warburg discovered that tumor cells exhibit unique reprogramming phenotypes,[1–3] a phenomenon he named the "Warburg effect".[4,5] One of the main characteristic of Warburg effect is that, despite sufficient oxygen supply, cancer cells still produce energy through glycolysis instead of relying on mitochondrial oxidative phosphorylation, leading to elevated glucose uptake as well as ATP and lactic acid accumulation in cancer cells.[4,6] Although more ATP can be produced by oxidative phosphorylation, precursors or intermediates produced during glycolysis by the pentose phosphate pathway, the hexosamine pathway, and the serine/glycine biosynthesis pathway can provide carbon sources for various biosynthesis reactions, thereby meeting the needs for rapid DNA replication.[7–11] Glycolysis produces less reactive oxygen species (ROS) when compared to mitochondrial oxidative phosphorylation, which can induce tumor cell apoptosis or senescence under oxygen stress.[12] In addition, the lactic acid produced by glycolysis can lower the pH of the extracellular matrix (ECM).[13] An acidic microenvironment promotes tumor cell invasion, metastasis, and enhances their resistance to radiotherapy.[14,15] Therefore, it is beneficial for tumor cells to rely on

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glycolysis to meet their energy needs because the Warburg effect is an optimized way through which tumor cells stimulate growth by cell stress.

Circular RNAs (circRNAs) were first discovered in ribonucleic acid (RNA) viruses in 1976,[16] followed by their discovery in form of endogenous RNA splicing products in eukaryotes in 1979.[17] circRNAs were originally thought to result from RNA splicing errors, however, this theory was negated by the discovery of a large number of circRNAs in mammalian cells using RNA sequencing (RNA-seq) technology and bioinformatics. Salzman et al[18] confirmed that circRNA is the main transcript for a variety of human cell types. Jack et al[19] identified more than 25,000 circRNAs in human fibroblasts, implying that they are stable, conservative, and non-random products of RNA splicing, which may be associated with complementary ALU repeats in adjacent introns. These findings reveal dynamic expression patterns of circRNAs in various developmental stages and physiological conditions. For example, they serve as scaffolds in the assembly of protein complexes,[20,21] and are also involved in; the isolation of proteins from their natural subcellular localization,[22,23] regulating the expression of parental genes,[24–27] regulating other splicing processes,[28,29] RNA-protein interactions,[30] and act as microRNA (miRNA) sponges[31–33] (Figure 1).

The most direct strategy for manipulating glucose metabolism is by affecting metabolic enzymes or kinases. Some signaling pathways, which play an important role in glucose metabolism can also be manipulated. Alterations in mRNA and protein levels are associated with glucose metabolism reprogramming in tumor cells.[34–36] This implies that glycolytic enzymes and signaling pathways may be targets for cancer treatment.[34,37] (Figure 2 and Figure 3).

Therefore, this review focuses on the mechanisms through which circRNAs regulate glucose metabolism, with the aim of elucidating on the complex cancer metabolism regulatory networks and providing a better theoretical basis for clinical diagnosis and treatment.

Table 1 summarizes circRNAs and their targets in the regulation of glucose metabolism in cancer.

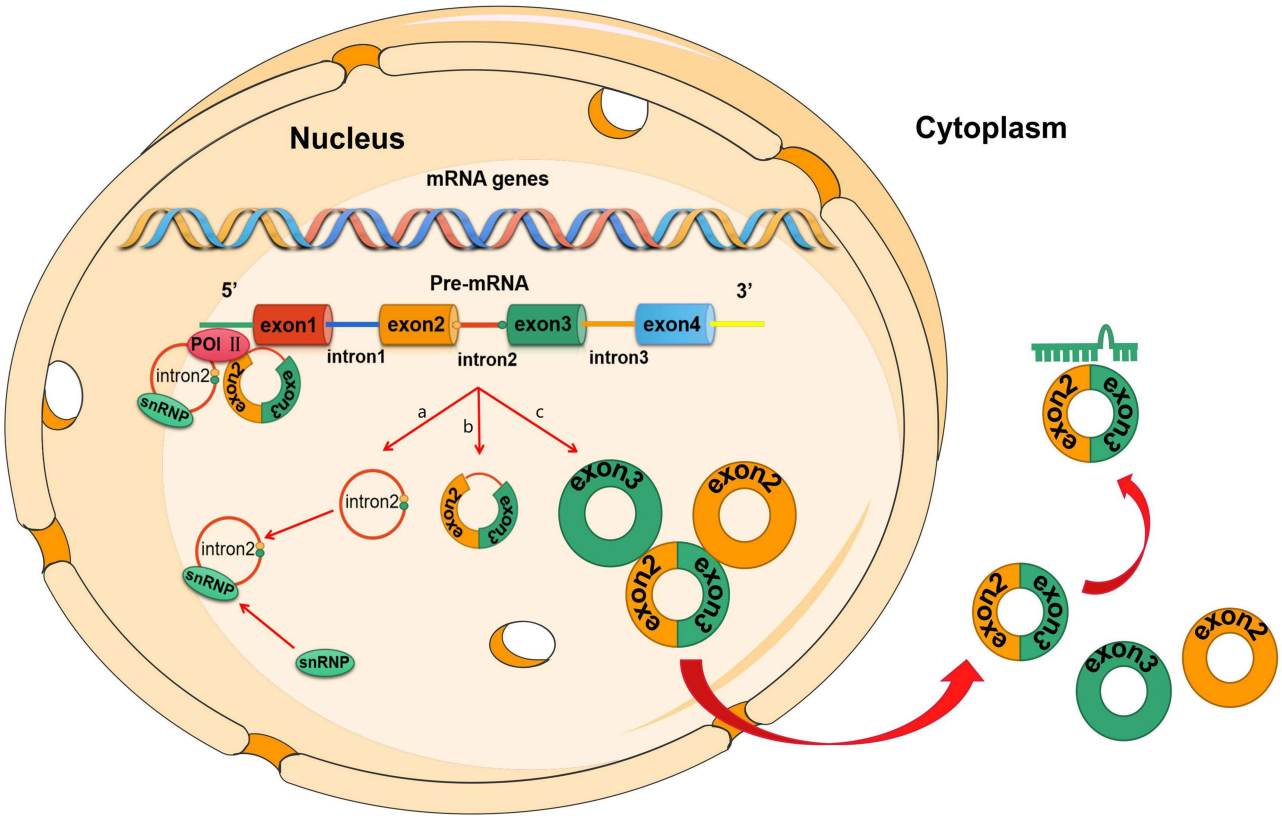

Figure 1 Biogenesis of circRNAs. (**A**) Intron cyclization: intron is cleaved from the pre-mRNA to form a ciRNA; (**B**) intron pairing-driven circularization: intronic complementary base-pairs bring adjacent two exons close together. The exons and introns are then spliced by spliceosomes to form circRNAs; (**C**) Lariat-driven circularization: this model requires covalent binding between the splicing donor and the splicing acceptor, thereby forming an exon-containing lariat.

Table 1 CircRNAs and Their Targets in the Regulation of Glucose Metabolism in Cancer

Items	Target	CircRNA	Tumor Type	Effect on Glycolysis	Type of Study	References
GLUT	GULT1	Circ0072995	Breast cancer	Up	In vitro, in vivo	[42]
		CircKLHL24	Breast Cancer	Down	In vitro, in vivo	[135]
		CircACACA	Non-small-cell lung Cancer	Up	In vitro, in vivo.	[83]
		Circ0000376,	Non-Small Cell Lung Cancer	Up	In vitro, in vivo	[136]
		Circ0002130	Non-Small Cell Lung Cancer	Up	In vitro, in vivo	[137]
		Circ100290	Oral squamous cell carcinoma	Up	In vitro	[41]
		CircKIAA0907	Oral squamous cell carcinoma	Down	In vitro, in vivo	[138]
		Circ0000140	Oral squamous cell carcinoma	Down	In vitro, in vivo	[139]
		CircFAT1	Colorectal Cancer	Down	In vitro, in vivo	[140]
		CircDENND4C	Colorectal cancer cells	Up	In vitro, in vivo	[141]
		Circ0007534	Colorectal cancer	Up	In vitro, in vivo.	[43]
		CircPTN	Glioma	Down	In vitro, in vivo	[142]
		CircTADA2A	Lung cancer	Up	In vitro, in vivo	[50]
		CircPDE5A	Neuroblastoma	Up	In vitro, in vivo.	[143]
		Circ0105346	Osteosarcoma	Up	In vitro, in vivo.	[144]
		CircPRKCI	Hepatocellular carcinoma	Down	In vitro	[145]
	GULT3	CircMYLK	Non-Small Cell Lung Cancer	Up	In vitro,	[51]
Enzymes	HK1	CircCDR1	Nasopharyngeal carcinoma	Up	In vitro, in vivo.	[26]
	HK2	CircZNF609	Nasopharyngeal carcinoma	Up	In vitro, in vivo.	[55]
		CircBICD2	Oral squamous cell carcinoma	Up	In vitro, in vivo	[147]
		CircPVT1	Oral squamous cell carcinoma	Up	In vitro, in vivo.	[54]
		CircMDM2	Oral squamous cell carcinoma	Up	In vitro, in vivo	[148]
		CircRNF20	Breast cancer	Up	In vitro, in vivo.	[57]
		Circ0069094	Breast cancer	Up	In vitro, in vivo.	[149]
		Circ0008039	Breast cancer	Up	In vitro, in vivo.	[150]
		CircRAD18	Breast Cancer	Up	In vitro, in vivo	[151]
		CircNFIX	Non-Small Cell Lung Cancer	Up	In vitro, in vivo	[152]
		Circ0008928	Non-small Cell Lung Cancer	Up	In vitro	[153]
		CircPRMT5	Hepatocellular Carcinoma	Up	In vitro, in vivo	[154]
		Circ0046599	Hepatocellular Carcinoma	Up	In vitro, in vivo	[155]
		CircZNF652	Hepatocellular Carcinoma	Up	In vitro, in vivo	[156]
		Circ009157	Hepatocellular Carcinoma	Up	In vitro	[157]
		CircTTBK2	Glioma	Up	In vitro, in vivo	[158][
		CircNFIX	Glioma	Up	In vitro, in vivo.	[58]
		Circ0001421	Lung cancer	Up	In vitro, in vivo	[159]
		Circ0080145	Chronic Myeloid Leukemia	Up	In vitro, in vivo	[160]
		Circ0001776	Endometrial cancer	Down	In vitro, in vivo	[161]
		Circ0006168	Esophageal cancer	Up	In vitro	[62]
		CircSLAMF6	Gastric cancer	Up	In vitro, in vivo	[162]
		Circ0016347	Osteosarcoma	Up	In vitro, in vivo.	[163]
		CircCDKN2B-AS1	Cervical squamous cell carcinoma	Up	In vitro, in vivo	[164]
		CircZNF609	Prostate Cancer	Up	In vitro, in vivo.	[56]
	PK	Circ0025033	Ovarian cancer	Up	In vitro, in vivo.	[63]
	PKM2	CircMAT2B	Hepatocellular carcinoma	Up	In vitro, in vivo.	[61]
		Circ0057553	Prostate Cancer	Up	In vitro, in vivo	[165]
		CircFOXM1	Melanoma	Up	In vitro, in vivo	[166]
		CircPOSTN	Glioma	Up	In vitro, in vivo.	[68]
		Circ0005963	Colorectal cancer	Up	In vitro, in vivo	[167]

(*Continued*)

Table 1 (Continued).

Items	Target	CircRNA	Tumor Type	Effect on Glycolysis	Type of Study	References
	LDHA	CircECE1	Osteosarcoma	Up	In vitro, in vivo.	[82]
		Circ0056285	Osteosarcoma Cells	Up	In vitro, in vivo.	[168]
		Circ0000735	Non-small cell lung cancer	Up	In vitro, in vivo.	[169]
		CircARHGAP10	Non-small cell lung cancer	Up	In vitro, in vivo	[170]
		CircMEMO1	Non-small cell lung cancer	Up	In vitro, in vivo	[171]
		Circ0001610	Endometrial carcinoma	Up	In vitro, in vivo.	[172]
		CircSEC24A	Cutaneous Squamous Cell Carcinoma	Up	In vitro, in vivo.	[173]
		CircDUSP16	Esophageal Squamous Cell Carcinoma	Up	In vitro, in vivo.	[174]
		Circ403658	Bladder cancer	Up	In vitro, in vivo	[175]
		CircMYC	Melanoma	Up	In vitro	[176]
		Circ0136666	Colorectal Cancer	Up	In vitro, in vivo	[177]
		CircGDI2	Oral Squamous Cell Carcinoma	Down	In vitro, in vivo	[178]
		Circ0000376	Gastric cancer	Up	In vitro	[179]
		Circ0004913	Hepatocellular Carcinoma	Up	In vitro, in vivo	[180]
		CircYY1	Breast Cancer	Up	In vitro, in vivo.	[181]
		CircSMARCA5	Prostate Cancer	Up	In vitro, in vivo.	[182]
		CircPRKCI	Papillary thyroid cancer	Up	In vitro, in vivo.	[183]
PDK	PDK1	CircCNST	Osteosarcoma cells	Up	In vitro, in vivo.	[73]
		Circ0002711	Ovarian cancer	Up	In vitro, in vivo.	[74]
		CircEPHB4	Gliomas	Up	In vitro, in vivo.	[75]
	PDK2	Circ0091579	Hepatocellular carcinoma	Up	In vitro, in vivo.	[76]
	PDK4	CircCCDC66	thyroid cancer	Up	In vitro	[77]
Oncogenes	C-Myc	CircENO1	Lung adenocarcinoma	Up	In vitro, in vivo.	[87]
	ENO1	CircCUX1	Neuroblastoma	Up	In vitro, in vivo.	[90]
		CircABCB10	Breast Cancer	Up	In vitro	[69]
		CircSEMA5A	Bladder cancer	Up	In vitro, in vivo	[184]
HIF	HIF-1a	CircNRIP1	Gastric Carcinoma	Up	In vitro	[99]
		CircMAT2B	Gastric Carcinoma	Up	In vitro, in vivo	[185]
		CircDENND4C	Breast cancer	Up	In vitro, in vivo.	[98]
		CircZFR	Breast cancer	Up	In vitro, in vivo	[186]
		CircPITX1	Glioma	Up	In vitro, in vivo	[187]
		CircSEPT9	Glioma	Up	In vitro, in vivo.	[188]
		Circ03955	Pancreatic cancer	Up	In vitro, in vivo.	[189]
		CircAKT3	Lung cancer	Down	In vitro, in vivo	[190]
		CircSLC25A16	Non-small cell lung cancer	Up	In vitro, in vivo	[191]
Wnt/Snail	EMT	CircFNDC3B	Colon cancer	Down	In vitro, in vivo	[110]
		Circ0072387	Oral Squamous Cell Carcinoma	Down	In vitro, in vivo	[111]
		Circ0035483	Renal Cell Carcinoma	Up	In vitro, in vivo.	[192]
		Circ0085616	Cervical Cancer	Up	In vitro, in vivo	[193]
		Circ0001721	Osteosarcoma	Up	In vitro, in vivo	[194]
		Circ0000517	Hepatocellular carcinoma	Up	In vitro, in vivo	[195]
PI3K/AKT/ mTOR		CircRHOBTB3	Ovarian cancer.	Down	In vitro	[121]
		CircHIPK3	Lung cancer	Up	In vitro, in vivo	[120]

CircRNAs Regulate the Enzymes, Regulatory Molecules, and Oncogenes Involved in Glucose Metabolism in Cancer

CircRNAs Regulate Glucose Uptake by Altering the Expression of Glucose Transporter (GLUT)

Glucose transporter (GLUT) is a membrane protein that regulates cellular glucose metabolism. Under normal physiological conditions, GLUT promotes passive glucose transport by quickly transporting glucose from capillaries to cells. Among the 14 identified GLUT subtypes, GLUT1, GLUT3, and GLUT4 are up-regulated in malignant tumor cells, implying that they accelerate glucose transport in malignant tumors.[38,39] This feature has been used in positron emission tomography for non-invasive diagnostic imaging of human cancer using radiolabeled glucose analogues and computer tomography.[40]

CircRNAs are involved in the regulation of GLUT1 expression. Circ100290, as a competitive endogenous RNA (ceRNA), elevates GLUT1 expression through mir-378a, thereby promoting glycolysis, proliferation, and invasion of oral squamous cell carcinoma cells.[41] Qi et al[42] found that circ0072995, as a type of carcinogenic circular RNA, induces malignant phenotype of cells through the mir-149-5p/SHMT2 axis. Therefore, circ0072995 enhances glucose uptake and lactic acid production, and promotes anaerobic glycolysis in breast cancer by promoting GLUT expression. circ0007534 significantly regulates protein levels of glycolysis-related genes (*GULT1*) in colon cancer through the mir-613/SLC25A22 axis, thereby affecting the efficiency of glycolysis and colon cancer cell progression.[43] Propofol is the most widely used intravenous anesthetic in clinical surgery.[44,45] In addition to various anesthetic effects, propofol exhibits anti-cancer affects[46,47] against breast cancer[48] and stomach cancer.[49] Zhao et al[50] found that, propofol regulates protein levels of GLUT1 by regulating circTADA2A expression through the mir-455 - 3p/FOXM1 axis, which suppresses glucose uptake by cancer cells, lactic acid production, and extracellular acidification, and inhibits lung cancer cell proliferation. Xiong et al[51] reported that in non-small cell lung cancer cells (NSCLC), circMYLK is a molecular sponge for miR-195-5p while glucose transporter member 3 (GLUT3) is the target gene of miR-195-5p. Suppression of GLUT3 reduces lactic acid production in cancer cells. The decrease in lactic acid production was attributed to a decreased efficiency of aerobic glycolysis or the conversion of pyruvate to acetyl-CoA (Figures 2 and 4).

CircRNA Affects Glycolysis by Regulating Enzymes or Kinases

Hexokinase (HK) is the first rate-limiting enzyme in the glycolytic pathway and is associated with cancer progression.[52] It transforms glucose into 6-phosphate-glucose and promotes glucose transport into cells by glucose transporter 1 (GLUT1). In addition to the widely expressed HK1, cancer cells also overexpress HK2, which can enhance glycolysis.[53]

Expression of circPVT1 in highly invasive oral squamous cell carcinoma (OSCC) cells was found to be significantly elevated, and was associated with increased HK2 expression and suppressed mir-106a-5p expression.[54] In vitro, HK2 was shown to be a direct target of mir-106a-5p while circPVT1 reversely regulated mir-106a-5p at the transcriptional level. These findings show that mir-106a-5p is a key factor between circPVT1 and HK2. In nasopharyngeal carcinoma and prostate cancer cells, the circRNA of the ZNF609 gene promotes cancer cell occurrence and development by up-regulating HK2 expression. Knockout of the *HRAS* gene inhibited HK2 expression and suppressed glucose consumption, lactate production, and ATP levels in nasopharyngeal carcinoma cells.[55] Besides, the *HK2* gene is the target of mir-501-3p in prostate cancer cells. Transfection of mir-501-3p can inhibit the expression of the HK2 protein, promote glycolysis, and improve radiation resistance of prostate cancer cells.[56] In addition to the above-mentioned circRNA, circRNF20 occurs in breast cancer,[57] circENO1 in lung adenocarcinoma,[57] and circNFIX in glioma.[58] These circRNAs can affect HK2 expression and promote cancer cell progression (Figures 2 and 4).

Pyruvate kinase (PK) is the last rate-limiting enzyme in glycolysis. Its activity can be affected by metamorphism and covalent modification. PK converts phosphoenolpyruvic acid (PEP) to pyruvic acid, where the first and second steps consume ATP while the last step produces ATP. Currently, four PK isoenzymes have been identified: M, K, L, and R types. The aberrant expression of pyruvate kinase M2 (PKM2) is very common in tumor cells.[59] It is a splicing isoform of a dimeric pyruvate kinase involved in aerobic glycolysis, and it determines the proportion of carbon derived from glucose during energy production

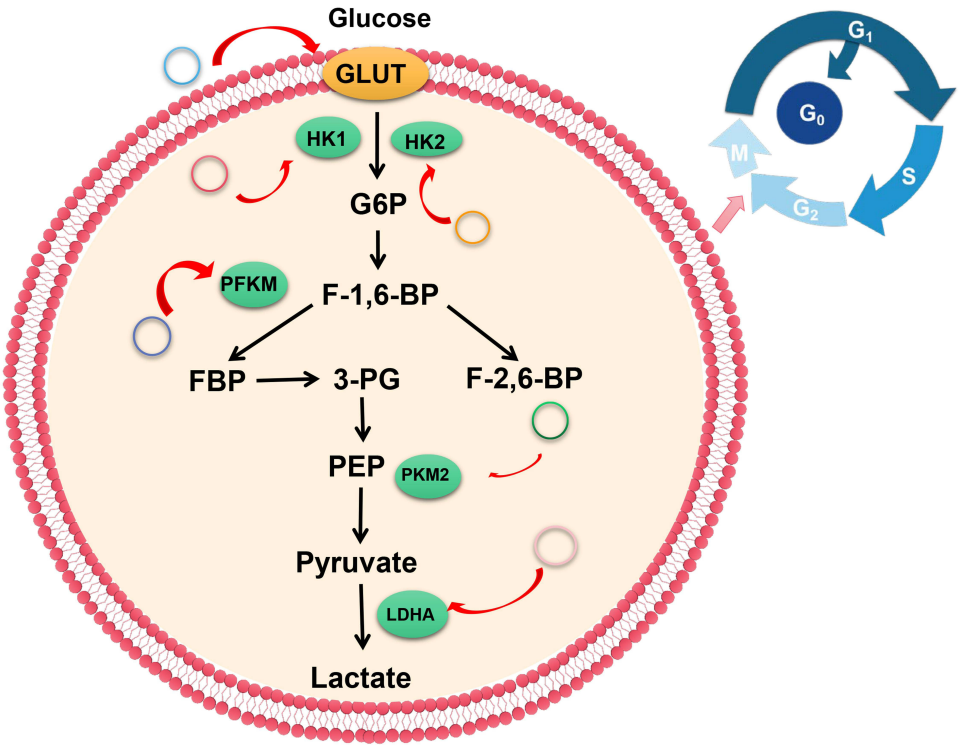

Figure 2 CircRNAs regulate the molecules involved in glucose metabolism in cancer. CircRNAs regulate glucose uptake and glycolytic flux by modulating GLUTs and glycolic enzymes.

through glycolysis.[60] Dysregulated circRNAs in cancer influence PKM2 expression. In liver cancer, mir-338 - 3p was found to be down-regulated despite PKM2 overexpression.[61] This can be attributed to elevated expressions of circular RNA MAT2B, which acts as a molecular sponge for capturing mir-338-3p. Therefore, the MAT2B/mir-338-3p axis promotes glycolysis and liver cancer progression under hypoxic conditions by regulating PKM2 expression. Furthermore, circ0006168 regulates the mir-384/RBBP7 axis by activating the S6K/S6 pathway, and regulates PK protein levels in order to promote esophageal cancer cell growth, migration, invasion, and glycolysis.[62] Hou et al[63] knocked out circ0025033 in ovarian cancer cells and found that glucose consumption and lactic acid production were inhibited while si-circ0025033 transfection significantly suppressed PKM2 expression when compared to si-NC transfection (Figures 2 and 4).

Lactate dehydrogenase A (LDHA) is one of the subunits of lactate dehydrogenase (LDH) isoenzyme, which was first identified as one of the glycolytic genes induced by the *myc* gene.[64] Its expression levels are associated with survival outcomes of various cancers, and it modulates tumor cell proliferation and invasion.[45,65] Moreover, it can catalyze reversible conversion of pyruvate and lactic acid, resulting in lactic acid accumulation, which leads to tumor microenvironment acidification and enhanced tumor invasion. Secreted lactic acid can also be absorbed by adjacent tumor-associated stromal cells, ultimately producing pyruvate.[66,67] CircRNAs modulate glycolysis by regulating the expression of the LDHA gene. Long et al[68] reported that circPOSTN elevates the expression of LDHA in glioma cells. The underlying mechanism involves lactic acid production regulation through the circPOSTN/mir-361-5p /TPX2 axis, which provides an acidic environment for cells and eventually, promotes glioma cell proliferation and invasion. circABCB10 knockout in breast cancer cells negatively regulates glycolysis through the mir-223 - 3P/PFN axis, thereby reducing glucose consumption and lactic acid production, suppressing LDH-A activity and ATP level, promoting infrared treatment sensitivity, and providing a new direction for breast cancer radiotherapy[69] (Figure 2).

The pyruvate dehydrogenase complex (PDC) is essential in metabolic homeostasis and is regulated by pyruvate dehydrogenase kinases (PDKs). The PDKs control PDC activity by phosphorylating its specific serine residues and, subsequently, deactivating the system if present in excess. There are four known isoforms of PDK's (PDK1, PDK2,

PDK3, and PDK4), that have different binding affinities to the complex.[70] The isozymes bind phosphates to specific serine residues present within the α-subunits of the E1 of the complex.[71,72] Hu et al[73] reported that Circ-CNST regulates PDK1 expression by sponging miR-578 and glucose consumption. Moreover, lactate production and ATP/ADP ratios were found to be suppressed in Circ-CNST upregulated osteosarcoma cells. Xie et al[74] knocked out Circ_0002711 in ovarian cancer cells and found that they could significantly inhibit glucose consumption, lactic acid production and PDK1 expression by modulating the miR-1244/ROCK1 axis. In gliomas, CircRNA EPHB4 modulates significantly promoting glucose consumption, lactate production and PDK1 expression levels by sponging miR-637.[75] In Hepatocellular carcinoma, Circ0091579 enhances PDK2 protein expression under hypoxic stress conditions and promotes glucose uptake as well as lactic acid production.[76] Moreover, PDK4 protein expression is enhanced by CircCCDC66 in thyroid cancer[77] (Figures 3 and 4).

CircRNA Affects Glycolysis by Regulating Oncogenes

Molecular mechanisms of metabolic abnormalities are associated with oncogene activation or tumor suppressor loss, eventually leading to elevated expression levels of hypoxia inducible factor 1α (HIF-1α) or the c-Myc oncogene. Studies[64,78,79] have shown that aberrant regulation of the MYC oncogene is common during tumorigenesis. Notably, c-Myc is a transcription factor that is encoded by the MYC oncogene. Under normal oxygen conditions, regulation of the glycolytic genes by c-Myc promotes glucose metabolism as well as cell growth and proliferation.

Kim et al[80] reported that dysregulated hypoxia-inducible factor-1 (HIF-1) can cooperate with dysregulated c-Myc to induce catalase hexose kinase 2 (the first key enzyme of glycolysis) and inactivate lactate dehydrogenase, thereby suppressing mitochondrial respiration and promoting glycolysis. TXNIP is an effective negative regulator of glucose

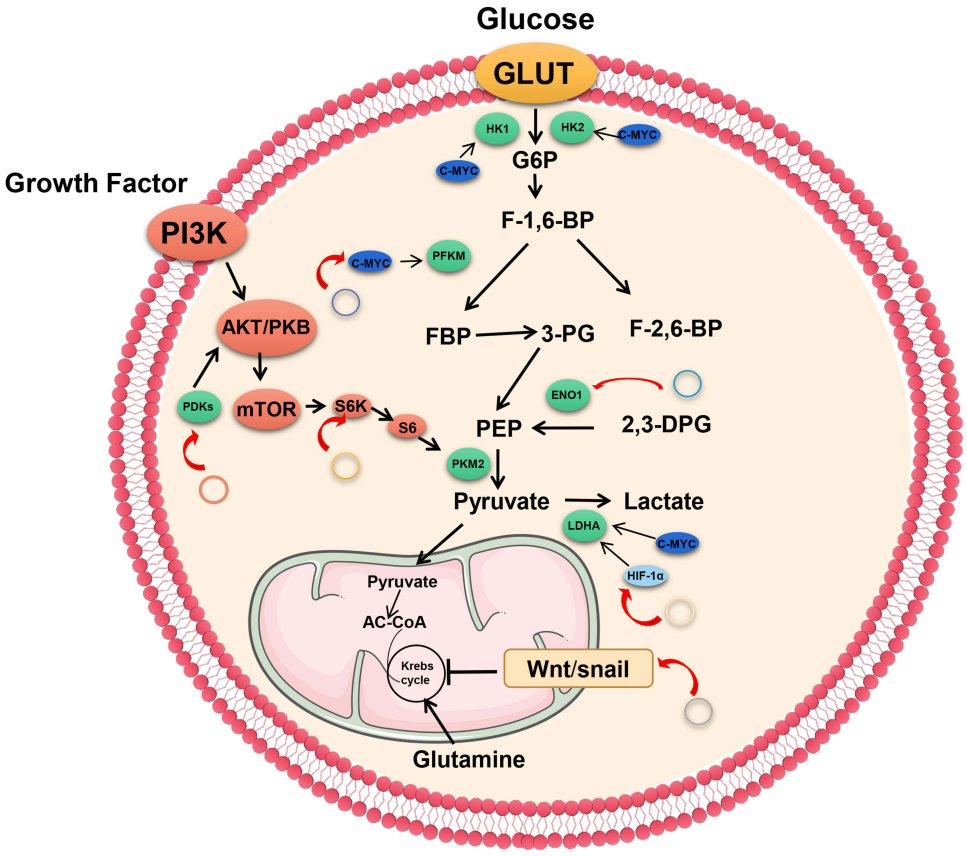

Figure 3 Role of CircRNA-mediated HIF and S6K/S6 pathways in glucose metabolism in tumor cells. CircRNAs can regulate HIF-1α protein synthesis and stability, thereby modulating HIF-1-mediated metabolic reprogramming. HIF-1α plays a key role in stimulating glycolic enzymes and in blocking mitochondrial activity. CircRNAs can also regulate S6K pathways. S6K may elevate oxidative phosphorylation by enhancing metabolic coupling between glycolysis and oxidative phosphorylation and increases glucose uptake and flux.

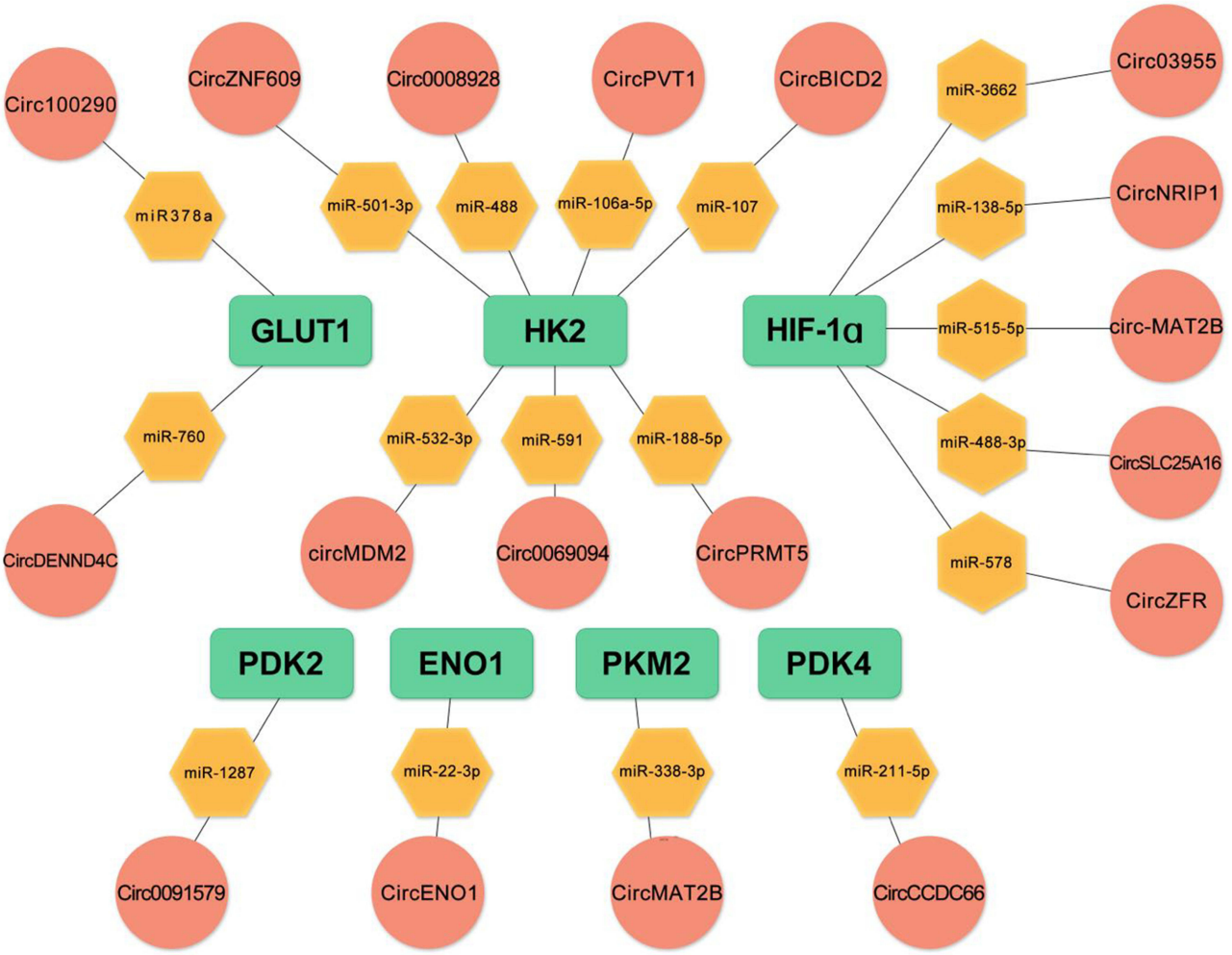

Figure 4 The ceRNA network of circRNA-miRNA-mRNA. Spherical indicate circRNA, diamond represent miRNA, and rectangles indicate mRNA.

uptake and aerobic glycolysis.[81] Shen et al[82] found that mRNA and protein expression levels of TXMP were significantly elevated in osteosarcoma cells with circECE1 knock out when compared to control cells. This indicates that TXNIP is mainly regulated by circECE1 transcription. Moreover, circECE1 interacts with c-Myc to prevent spop-induced c-Myc ubiquitination and degradation, and activates the c-Myc-TXNIP signal-regulated Warburg effect. There is a feedback loop between c-Myc and circECE1 - TXNIP, which regulates c-Myc protein expression and glucose metabolism. Circ-ACACA regulates the PI3K/PKB signaling pathway in non-small cell lung cancer (NSCLC) cells by interacting with MIR-1183, and suppresses protein expression levels of *c-Myc, MMP9*, and *GLUT-1* genes in tumor cells, thereby promoting glycolysis.[83]

Enolase (ENO1) is a glycolytic enzyme that acts as a metabolic tumor promoter of the Warburg effect in cancer cells. It plays a vital role in aerobic glycolysis by converting 2-phosphoglyceride into phosphoenolpyruvate.[84–86] In lung adenocarcinoma, ENO1 is the main target of miR-22-3p, and miR-22-3p transfection can suppress ENO1 protein expression. Therefore, circRNA of the *ENO1* gene elevates protein expression levels of ENO1 as well as promote glycolysis and tumor progression of lung adenocarcinoma by up-regulating miR-22 - 3p.[87]

Phosphate isomerase (PI) is a cytoplasmic enzyme responsible for catalyzing mutual conversions between glucose-6-phosphatase and fructose-6-phosphatase. Therefore, it plays a key role in the glycolytic pathway.[88] Phosphoglycerate kinase 1 (PGK1) contributes to ATP production and is involved in tumor occurrence and development.[89] In addition, overexpression or knockdown of p200 CUX1 (CUX1) elevated or suppressed expression levels of p110 CUX1, ENO1, glucose-6-phosphate isomerase (GPI), or PGK1.[90] The binding of circ-CUX1 to the RRM region of EWSR1 leads to EWSR1-mediated MAZ

reverse activation, implying that the circ-CUX1/ EWSR1/ MAZ axis promotes aerobic glycolysis and tumor progression (Figures 3 and 4).

CircRNAs Affect Glucose Metabolism by Regulating Cancer-Associated Signal Pathways

The HIF Signaling Pathway

Hypoxia inducible factor (HIF) is a nuclear transcription factor produced by cancer cells that have adapted to hypoxic environments. HIF1 is an oxygen-sensitive transcription complex composed of the oxygen regulatory subunit (HIF-1a) and the constitutive expression subunit (HIF-1b). Under hypoxia stress and PI3K activation, HIF-1a combines with the HIF-1b dimer to form active HIF-1 complexes, which regulate the transcription of various genes by binding hypoxia response elements.[91] In a hypoxic environment, most tumor cells carry out aerobic glycolysis, thereby promoting the expression of glucose transporters, which increase glucose uptake by activating HIF-1.[92] Moreover, it increases the expression of glycolytic enzymes,[93,94] inhibits oxidative phosphorylation,[95] and up-regulates LDHA, resulting in an acidic tumor microenvironment.[93,96,97] In breast cancer, circDENND4C and HIF-1a form a positive feedback loop, which contributes to the Warburg effect. Under hypoxic stress conditions, elevated HK2, MMP9, and MMP2 protein expressions promote glucose uptake and lactic acid production. In the hypoxia-inducible chain, circDENND4C, a direct transcription target of HIF-1 was shown to promote glycolysis by elevating HK2, MMP9, and MMP2 levels. However, this effect was reversed by ectopic expressions of HIF-1a, indicating that the function of circDENND4C was dependent on HIF-1.[98] Xu et al[99] showed that circNRIP1 sponged miR-138-5p through HIF-1α dependent glucose metabolism, thereby maintaining the resistance of gastric carcinoma (GC) cells to 5-FU under hypoxia. Therefore, the combination of targeted circNRIP1 and 5-FU can significantly improve the prognosis of GC patients (Figures 3 and 4).

The Wnt/Snail Signaling Pathway

Wnt signaling regulates embryonic development and its imbalance is closely associated with the occurrence of many malignant tumors (including breast and colon cancers). Moreover, it induces snail-dependent epithelial-mesenchymal transition (EMT), which is the main cause of tumor invasion and metastasis.[100–104]

Metabolic changes can control the EMT process and trigger tumor malignancies, commonly referred to as the Warburg effect.[105–107] Su et al[108] revealed that Wnt inhibits mitochondrial respiration by inhibiting cytochrome C oxidase and promotes glycolysis by inducing pyruvate carboxylase (a key peroxidase). This process depends on the β-catendon/T cytokine 4/Snail signaling pathway. Inhibition of E-cadherin inhibits mitochondrial respiration and stimulates glycolysis through snail activation, implying that EMT contributes to Wnt/snail-mediated regulation of mitochondrial respiration and glucose metabolism. FBP1 is one of the gluconeogenesis-related restriction enzymes that modulates glucose metabolism.[109] Pan et al[111] identified a novel protein encoded by circFNDC3B, which inhibits tumor progression and epithelial-mesenchymal transition in colon cancer by alleviating the inhibitory effect of snail on the *FBP1* gene. Therefore, it has been postulated that circFNDC3B plays a tumor suppressor role through the snail/FBP1/EMT axis.[110] Han et al[111] found that hsa_circ_0072387 expression was significantly downregulated while miR-503-5p was upregulated in OSCC cells and tissues. The gain of hsa_circ_0072387 or knockdown of miR-503-5p was shown to suppress OSCC cell proliferation, migration and invasion, EMT, as well as glycolysis. hsa_circ_0072387 targeted miR-503-5p and inversely regulated it expression. Moreover, upregulation of miR-503-5p partially reversed the tumor suppressive effects of hsa_circ_0072387 on OSCC cells (Figure 3).

The PI3K/AKT/mTOR Signaling Pathway

The phosphoinositide 3-kinase (PI3K) signaling pathway is involved in glucose metabolism. PI3K indirectly elevates the expression of GLUTs and enzymes by modulating Akt and mammalian target of rapamycin (mTOR). Akt-related metabolic factors include apoptosis-related kinases and GLUTs. Activation of Akt can elevate cellular ATP production and oxygen consumption.[112] Akt regulates glycolysis and can elevate the expression of GLUTs[113] and glycolytic enzymes such as HK2, PKM2[112,114,115] or inhibit mitochondrial oxidative phosphorylation[116,117] or activate mTORC1, which in turn elevates HIF-1 levels.[118,119]

CircHIPK3 is upregulated in lung cancer and promotes glucose uptake and utilization during aerobic glycolysis by enhancing Akt phosphorylation and activating the mTOR

signaling pathway, resulting in the upregulation of HK2.[120] Besides, Yalan et al found that CircRHOBTB3 plays a suppressor role and inhibits tumorigenesis by inactivating the PI3K/AKT pathway in ovarian cancer. Lentivectors for short hairpin RNA (shRNA) against circRHOBTB3 (sh-circRHOBTB3) or pcDNA-circRHOBTB3 were used to downregulate or upregulate circRHOBTB3 expression in an animal tumor model. It was found that the protein expressions of GLUT1, HK2 and LDHA were altered.[121](Figure 3).

Therapeutic Potential of CircRNA in Targeted Cancer Treatment

High rates of aerobic glycolysis in cancer cells are important for proliferation. Although oxidative phosphorylation is more beneficial for ATP production, high ATP production rates but at low efficiencies is uncommon in cancer cells. Instead, cancer cells may benefit from elevated levels of glycolysis intermediates such as nucleotides, amino acids, lipids, and NADPH.[122]

Identifying key nodes in the pathway network that regulates aerobic glycolysis can lead to the discovery of new targets for anti-tumor therapy. Among the various enzymes involved in the glycolysis cascade, GLUT-1, HK2, LDHA, and PKM2 are potential targets because they are overexpressed in cancer cells.[123–126] In addition, targeting the Warburg effect through precision medicine, a multi-pronged approach, may be an effective anti-cancer treatment strategy. For example, the Warburg effect was reversed in lung adenocarcinoma cells by inhibiting the EDFR signaling pathway.[127] Another treatment strategy involves combining targeted glycolysis drugs and mTOR inhibitors to prevent metabolic reprogramming from inducing cancer cell apoptosis.[128] For instance, the combination of acarbinidine (AICAR) and methotrexate (glucosamine) reversed the Warburg effect in MCF-7 breast cancer cells.[129] Although single drug therapy may induce resistance, combined therapy can induce AMPK and FOX1 expression, resulting in increased mitochondrial oxidative phosphorylation and reduced glycolysis. These metabolic changes indicate that the anti-Warburg effect prevents G1/S and G2/M transitions and slows cell cycle progression. A previous study performed on kidney and ganglion cell tumors reported germline mutations of succinate dehydrogenase and fumarate hydratase in the TCA cycle.[130] The role of one of these mutations is to activate HIF-1α-regulated glucose metabolism. Collectively, these findings imply that targeting glucose metabolism-related genes or pathways has great potentials in cancer treatment.

Interactions between circRNAs and key transcription factors or metabolic enzymes involved in glycolysis can effectively regulate glucose metabolism and promote tumor progression. In addition to these key molecules, other metabolic pathways are also crucial for glucose metabolism in cancer, especially the PI3K/AKT/ mTOR and the AMPK pathways. Considering glucose metabolism reprogramming, targeting circRNAs may have an important impact on cancer cell invasion and proliferation. Therefore, the circRNAs associated with aerobic glycolysis may be diagnostic and prognostic biomarkers for reprogramming glucose metabolism. Moreover, elucidation of circRNA-mediated glucose metabolism regulation in tumor cells may inform the development of circRNA inhibitors and prevent tumor progression.

Therefore, circRNA, as a regulator of metabolites, is more likely to provide novel targets for cancer treatment. However, there are many challenges associated with these methods. First, cells can recruit other glycolytic enzymes to promote glycolysis despite enzyme inhibitors being highly specific. Second, key target pathways must be identified. However, this may be difficult to achieve because of the phenotypic and functional heterogeneity between cancer and a single tumor. Third, it is necessary to clarify the toxic effects of inhibiting glycolytic enzymes in normal cells since aerobic glycolysis is a key process in immune and stem cells. Fluorodeoxyglucose positron emission tomography (FDG-PET) has previously been used to measure glucose metabolism, detect cancer, and predict prognosis.[131] Current methods, including positron emission tomography (PET), autoradiography and magnetic resonance imaging (MRI) can measure the primary metabolic rate of glucose. However, these methods are limited by the fact that they cannot distinguish between markers and intermediates.

Conclusion

Implementation of integrated treatment strategies for patients based on their genetic backgrounds is becoming a reality in cancer treatment. Advances in systematic biology, such as reconstruction of genome-scale metabolic models (GEMs), can enhance the accuracy of systematic assessment of cancer cell type-specific metabolic profiles.[132–134] Transgenic bio-integromics data can reveal the biomarkers and anti-metabolites of potential specific patients and cancer types. Furthermore, reprogrammed glucose metabolism is a recently identified marker for cancer

cells. Therefore, elucidation of the roles of circRNAs in glucose metabolism and their mechanisms will help in development of new strategies for controlling abnormal metabolic phenotypes and for inhibiting the Warburg effect.

Abbreviations

circRNA, Circular RNA; RNA-seq, RNA sequencing; miRNA, microRNA; ceRNA, competitive endogenous RNA; GLUT, glucose transporter; ROS, reactive oxygen species; ECM, extracellular matrix; HK, Hexokinase; OSCC, oral squamous cell carcinoma; PK, Pyruvate kinase; PEP, phosphoenolpyruvic acid; PKM2, pyruvate kinase M2; LDH, lactate dehydrogenase; HIF, Hypoxia induced factor; NSCLC, non-small-cell lung cancer; PDC, pyruvate dehydrogenase complex; PDKs, pyruvate dehydrogenase kinases; PI, phosphate isomerase; PGK1, Phosphoglycerate kinase 1; GPI, glucose-6-phosphate isomerase; GC, Gastric Carcinoma; EMT, epithelial-mesenchymal transition; FDG-PET, Fluorodeoxyglucose positron emission tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; GEM, genome-scale metabolic model.

Ethical Approval

Ethical approval was waived because human participants or animals were not involved in any way.

Consent for Publication

All authors read and approved the final manuscript for publication.

Authors' Statement

We hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere. We acknowledge that all authors sufficiently participated in the study and take responsibility for its content.

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Disclosure

All authors have no conflicts of interest to declare.

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