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REVIEW

Research Progress on the Regulation of Glycolysis in Gastric Cancer: Key Genes and Enzymes

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Abstract: Gastric cancer (GC) is a malignant tumor with extremely high morbidity and mortality. The incidence of GC in China is second only to that of lung cancer, seriously threatening human health and safety. Glycolysis is one of the important ways for cells to obtain energy and most tumor cells also rely on aerobic glycolysis, which plays a key role in the occurrence and development of GC. This article aims to systematically summarize the effects of key glycolytic enzymes and their upstream regulatory genes on GC, to provide a basis for revealing the pathogenesis of GC, and to evaluate potential therapeutic targets for GC.

Keywords: gastric cancer, glycolysis, gene regulation, enzyme regulation

Introduction

Gastric cancer (GC) is a common malignant tumor. In 2020, there were approximately over one million new cases worldwide, and the death toll reached as high as 769,000. It is the fourth most common malignant tumor and the third leading cause of death from malignant tumors in China, and also the second most common cancer in China.[1] Early symptoms of GC are more insidious, and most of the patients are in the middle or late stage when they are diagnosed, and the prognosis of patients is poor. As one of the high-incidence diseases, GC is caused by many etiologic factors.

First, Helicobacter pylori (Hp) infection is a class 1 risk factor for gastric carcinogenesis. Some prospective studies have shown that eradication of Hp is associated with a decreased risk of GC.[2] The inflammatory cascade reaction triggered by Hp infection can lead to chronic atrophic gastritis and intestinal metaplasia. This will lead to the loss of the main cells of the gastric mucosa, affect the secretory function, and ultimately promote the occurrence of GC. In addition, the environment is also one of the factors contributing to the development of GC. Epstein-Barr virus (EBV) infection, gastroesophageal reflux disease, alcohol consumption, cigarette smoking, chemical damage, diet, gender, obesity, gastric surgery, radiation, blood type and ethnicity interact with each other also influences the occurrence and development of GC.[3]

Secondly, dietary factors represent a major modifiable risk factor for GC. Given that dietary intake is the primary source of glucose, beyond glycogenolysis, specific dietary patterns significantly influence GC risk. High consumption of nitrite-preserved foods, high-salt diets, and processed meats can damage the gastric mucosa and promote carcinogenesis. Conversely, diets rich in fresh fruits and vegetables, which provide antioxidants and fiber, are associated with a reduced risk.[4] Furthermore, the role of chronic metabolic conditions linked to glucose homeostasis is increasingly recognized. Notably, diabetes mellitus, characterized by chronic hyperglycemia, has been identified as an independent risk factor for GC in epidemiological studies.[5] Hyperglycemia is postulated to promote cancer development by providing abundant glycolytic substrates, inducing oxidative stress, and activating inflammatory pathways, thereby creating a favorable microenvironment for tumor initiation and progression.[6]

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In addition, the formation of GC involves mutations, transcriptional abnormalities, and epigenetic alterations in a variety of related genes. Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene located in chromosome 17q21. HER2 serves as a cyber-receptor involved in signaling transduction in a variety of cancer cells, causing cancer cell proliferation.[7] It has been suggested that overexpression of HER2 may be involved in the early steps of GC.[8] Kanayama et al[9] found HER2 overexpression to be an independent risk factor for EGC recurrence. Microsatellite instability (MSI) has been associated with the formation of GC, possibly due to defective gene repair. MSI is also an important tumor factor in current clinical practice. Chakraborty et al[10] found that MSI might be one of the risk factors for GC. Bornschein J[11] reported that mutations in the CDH1 gene resulted in the down-regulation of the expression of E-calmodulin, which affected the signaling pathway of Hp adherence and post-infection and is closely related to GC. GC stem cells can also form tumors, and Han et al[12] isolated cells with specific markers from GC cells that could form tumors subcutaneously. Quante et al[13] found that bone marrow stem cells infected with Hp could converge on the gastric mucosa and induce atypical hyperplasia or even carcinoma under certain factors.

Clinical treatments for GC are mainly surgery, chemotherapy, radiotherapy, immunotherapy, traditional Chinese medicine. The comparison of treatment strategies for GC is shown in Table 1. At present, there are mainly two kinds of surgical treatments for GC: palliative surgery and radical surgery. Palliative surgery cannot remove the lesions of patients completely and is usually used to alleviate the complications of GC patients caused by perforation, obstruction, bleeding. Radical surgery, on the other hand, can remove the lesion radically, removing the tumor and metastatic lymph nodes as well as the affected infiltrating tissues together so that there will not be any tumor left. It is the only possible method to cure GC successfully, but it is more damaging to the human body and prone to surgical complications.[14] Chemotherapy can reduce the stage of the tumor mass and increase the R0 resection rate. It can control distant metastatic focus.[15] Thus, it enables the normal implementation of postoperative adjuvant treatment. Additionally, chemotherapy can determine the sensitivity of the tumor to chemotherapeutic drugs, which is conducive to the selection of chemotherapeutic drugs for postoperative adjuvant chemotherapy. Due to poor selectivity, chemotherapy drugs can cause a series of toxic and side effects on the human body, such as inflammatory responses, oxidative stress, and immune dysfunction. Due to the poor selectivity of chemotherapeutics, they can produce a series of toxic side effects on the human body, such as inflammatory reactions, oxidative stress and immune dysfunction.[16] The indications for radiotherapy include residual tumors, unresectable tumors, local recurrence, and distant metastatic tumors. Radiotherapy can relieve the local symptoms of patients.[17] However, it has relatively significant side effect such as inflammatory reactions, microvascular endothelial damage and fibrosis, and immune function disorders.[15] Immunotherapy is a new type of treatment that applies immune vaccines or anti-tumor antibodies to activate the immune system to resist tumors.[18] It can effectively prevent the recurrence and metastasis of cancer. However, it can also cause some immune-related adverse reactions, such as immune pneumonia and immune enteritis. Metastasis and invasion are the main characteristics of malignant GC cells, and they are also important reasons for the high mortality rate of GC.[19] The current clinical treatments for GC have various limitations, so it is urgent to explore the molecular mechanisms of GC pathogenesis and therapeutic means.

Table 1 Comparison of Treatments for GC

Treatment Strategy	Advantages	Drawbacks
Surgical treatment	Directly resect the lesion, control the disease state, and reduce the tumor burden.	Resect visible lesions, causing great damage to the body and being prone to complications.
Chemotherapy	Remove tiny cancerous focus.	Serious toxic and side effects.
Radiotherapy	Reduce the tumor volume and relieve the symptoms.	Side effects and immune system disruption.
Immunotherapy	Long-term treatment for tumor heterogeneity.	Expensive, immune-related side effects.
Targeted therapies	High-effective and low- toxicity.	Expensive.
Chinese medicine	Low toxic side effects.	Slow therapeutic effect.

The energy required for the life activities of normal human cells is mainly met by oxidative phosphorylation under aerobic conditions, and this metabolic energy production pathway is utilized more efficiently than glycolysis. Tumor cells are more inclined to utilize the glycolytic metabolic pathway energy production to satisfy cell growth and reproduction. A phenotype of tumor cells exhibiting high glycolysis under aerobic conditions has also been described.[20] The glycolytic pathway produces ATP at a much faster rate, providing the conditions necessary for the rapid proliferation of tumor cells. In addition, the products produced by glycolysis promote the proliferation and invasion of tumor cells. As an important metabolic pathway, glycolysis participates in cellular life activities by producing ATP and various metabolites. In GC, abnormal activation of glycolysis provides GC cells with sufficient energy and metabolites to promote their growth and proliferation. Increased aerobic glycolysis not only helps cancer cells to rapidly utilize glucose to generate abundant ATP, but also provides cancer cells with multiple components of cell synthesis through the pentose phosphate pathway, which is conducive to the survival and rapid proliferation of cancer cells.[21] In addition, the regulatory factors and intermediates of aerobic glycolysis can promote the invasion, metastasis, angiogenesis and epithelial-mesenchymal transition (EMT) of tumor cells by participating in signal transduction or epigenetic alterations, thus changing the tumor microenvironment.[22] The end product of glycolysis, lactic acid, greatly reduces the pH of the microenvironment of tumor cells, leading to poor intercellular connectivity and facilitating the migration of tumor cells.

Non-coding RNAs and membrane transporters play critical roles in regulating glycolysis. For instance, the single nucleotide polymorphism (SNP) rs61991156, located within the miR-379 gene, can influence glycolytic capacity.[23] Additionally, proteins from the SLC2A family are responsible for the facilitated diffusion of glucose across the plasma membrane, constituting the first and rate-limiting step of cellular glucose utilization.[24] The circRNA-related regulatory genes circRNA NRIP1[25] and circ PRDM5[26] can target and regulate the expression of miRNA in the body, and participate in the occurrence and development process of GC through metabolic signaling pathways. LncRNA-associated regulatory genes such as H19[27] and ABHD11-AS1[28] are highly expressed in tumor cells, which will promote important biological processes such as cell cycle, apoptosis, angiogenesis, invasion and metastasis of tumors.

Some related proteins in the glycolytic pathway, such as M2-type pyruvate kinase 2 (PKM2), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and hypoxia-inducible factor 1 alpha (HIF-1α), can regulate GC progression. Key regulatory enzymes in the glycolysis process, such as triosephosphate isomerase 1, pyruvate kinase M2, phosphoglycerate kinase, lactate dehydrogenase (LDH) and 6-phosphofructo-2-kinase 3, control the expression of signaling pathways by regulating related protein kinases and intermediate products in the glycolysis process, thereby promoting apoptosis, metastasis, proliferation and immune escape of GC cells. The key markers of cancer proliferation and metastasis are mainly the decrease of glucose content and the increase of lactate and glycolytic intermediates.[29] Therefore, the relationship between glycolysis and GC, and the mechanism of action of key glycolytic enzymes and their upstream regulatory factors are of great significance in revealing the pathogenesis of GC and providing a theoretical foundation for future research.

The Relationship Between Glycolysis and GC

Glycolysis is the main way that organisms obtain energy. The main pathways for the oxidative decomposition of sugars in organisms are anaerobic decomposition, aerobic decomposition, and the pentose phosphate pathway. A series of enzymes that catalyze the glycolytic reaction are present in the cytoplasm. Glycolysis is a common stage that all organisms must go through for the metabolic decomposition of glucose. Under aerobic conditions, organisms convert glucose into two molecules of pyruvate under the catalysis of the corresponding enzymes. Pyruvate is transferred to the mitochondria under the action of pyruvate dehydrogenase (PDH) and undergoes oxidative decarboxylation to form acetyl coenzyme A (CoA). Acetyl-CoA subsequently enters the tricarboxylic acid (TCA) cycle, generating a large amount of ATP to provide energy for the cell. Pyruvate dehydrogenase activity is phosphorylated and inactivated under anaerobic conditions. Mammals activate the anaerobic pathway by upregulating a series of key enzymes involved in glucose uptake, glycolysis, and the conversion of pyruvate to lactate. Compared with oxidative phosphorylation, the amount of ATP produced by glycolysis in the anaerobic direction is less.[30] Most tumor cells still rely on glycolysis for energy supply even when there is sufficient oxygen supply. This phenomenon is known as aerobic glycolysis or Warburg effect.[31]

Epstein et al[32] showed that compared with oxidative phosphorylation, the glycolytic pathway can better meet the increased energy demand of cancer cells. The increase in aerobic glycolysis can not only help cancer cells rapidly utilize glucose to produce abundant ATP. It can also provide various components for cell synthesis to cancer cells through the pentose phosphate pathway. This is beneficial to the survival and rapid proliferation of cancer cells.[33] The final product of glycolysis, lactic acid, can serve as a signaling molecule to upregulate the expression of matrix metalloproteinase-9 (MMP-9) and MMP-2. Thus, it degrades important components of the basement membrane, including type IV collagen, type VII collagen and glycoproteins, which makes the tumor more prone to metastasis, invasion, and migration.[34] CLDN9 enhances the glycolytic pathway of GC through the PI3K/AKT/HIF1α signaling pathway, promotes the lactation of PD-L1, and thereby inhibits the anti-tumor immunity of $CD8^+$ T cells.[35]

Research has found that lactic acid significantly enhanced the invasion and migration potential of lung cancer cells, and it was directly related to the activities of EMT and Snail protein.[36] Then, we explored the expression of some related genes and enzymes in the glycolytic pathway in the specimens of GC patients, explored the relationship between these genes, enzymes and GC, and evaluated their potential as therapeutic targets for GC.[37] The regulation effects of glycolysis-regulating genes and enzymes on GC cells are shown in Table 2 and Table 3.

Genes Regulating Glycolysis in GC

LncRNAs Regulating Glycolysis in GC

Long non-coding RNAs (lncRNAs) are a class of RNA transcripts that are more than 200 nucleotides in length but have no protein-coding potential. LncRNA can regulate gene transcription and mRNA translation by interacting with other components such as proteins, RNAs, and DNAs. Thus, lncRNA participates in the occurrence, development, metastasis and drug resistance of diseases.[38,61] H19 could influence the glycolysis process by regulating pyruvate dehydrogenase kinase 1 (PDK1) expression. Chen[27] et al found that low expression of H19 reduced the amounts of glucose and lactic acid consumed by GC cells. The H19 expression in GC cells was positively correlated with the expression levels of phosphoglycerate kinase 1 (PGK1) mRNA and protein. High expression of ABHD11-AS1 in GC cells could upregulate the expression level of c-Myc. By increasing the expression of c-Myc, it recruits downstream glycolytic target genes of c-Myc, thus affecting the occurrence of GC. Regulatory mechanism of lncRNAs regulating glycolysis on GC are shown in Figure 1.

Table 2 Role of Non-Coding RNA Regulating Glycolysis in GC

Non-coding RNA	Regulatory Gene	Mechanism of Action	References
lncRNA	H19	Directly control glycolytic enzymes; Affect GC by acting on the miR-19a-3p/PGK1 pathway.	[23,35–37]
	ABHD11-AS1	Synergistically regulate PDPK1 with miR-361-3p to promote the proliferation of GC cells.	[24,27,31,38,39]
circRNA	NRIP1	Adsorption of related miRNA, activation of AKT1/mTOR signaling.	[21,40–42]
	PRDM5	Interact with miR-485-3p; Regulate HK2 to inhibit glycolysis.	[22,43,44]
miRNA	rs61991156	Inhibit the occurrence of GC by regulating PKM2, a key enzyme in glycolysis.	[19,45,46]
	miR-129-5p	MiR-129-5p interacts with SLC2 to participate in PI3K-Akt and MAPK signaling pathways to regulate GC.	[20,47,48]

Table 3 Effects of Glycolysis-Regulating Enzymes on GC Cells

Regulatory Enzyme	Catalytic Reaction	The GC Impact	Bibliography
Pyruvate kinase	PEP → Pyruvate + ATP	Promoted GC cell proliferation and xenograft tumor formation.	[49–51]
Phosphoglycerate kinase	1,3-Diphosphoglyceric Acid → 3-Phosphoglyceric Acid + ATP	May act as a transcription factor during tumor cell migration; be associated with the metastasis of GC to the peritoneum and other metastatic dissemination pathways.	[52–55]
Lactate dehydrogenase	Pyruvate → Lactate + NAD^+	Regulate tumor cell migration and invasion; participate in tumor angiogenesis and tumor immune escape.	[56–58]
Fructose phosphate kinase	Fructose 6-phosphate → 1,6-di-phosphofructose + ADP	Induce cell cycle arrest, apoptosis and inhibit invasion of GC cells.	[59,60]

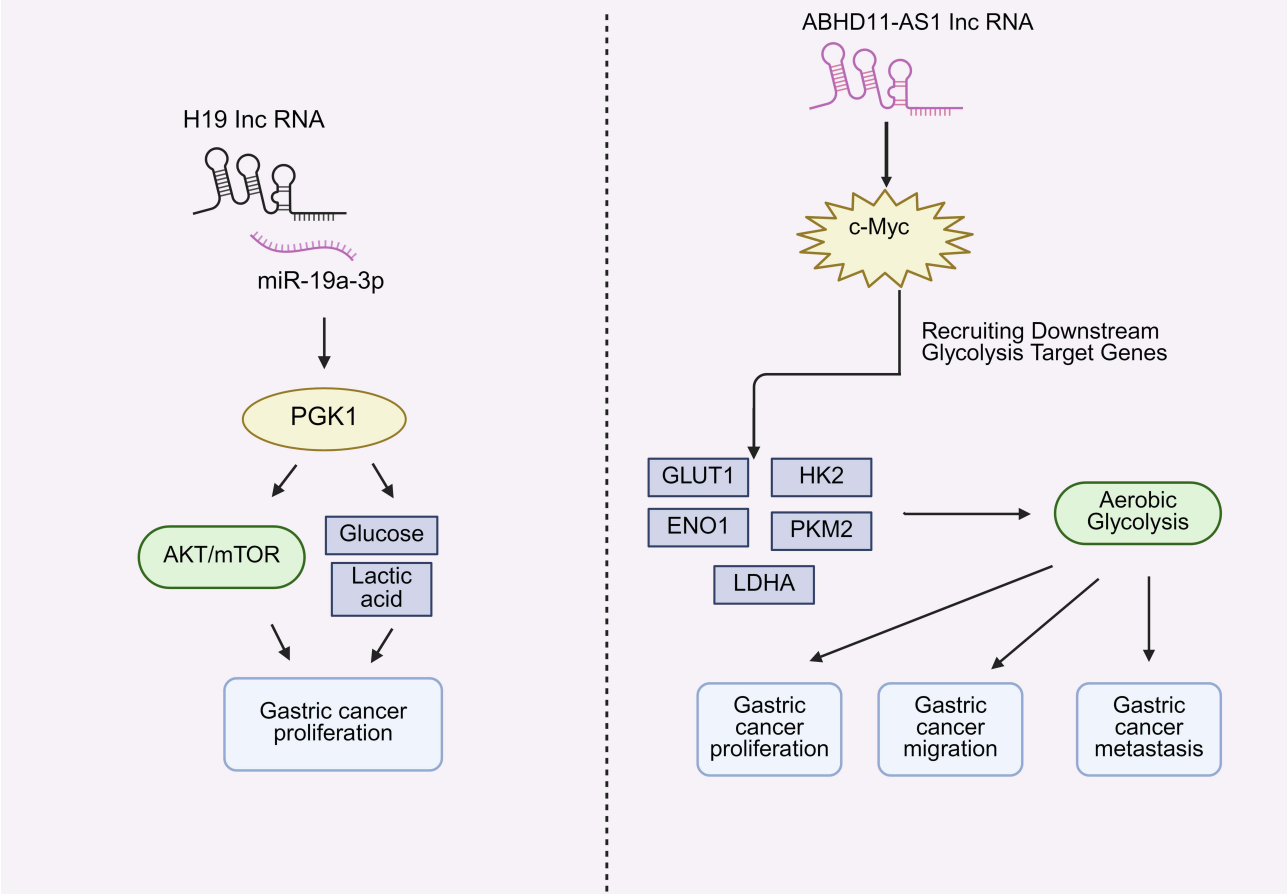

Figure 1 Regulatory mechanism of lncRNAs regulating glycolysis on GC.

H19

LncRNAs are involved in a variety of cancers and biological processes, including development, metastasis, drug resistance, metabolism, and immune escape.[62] LncRNAs can regulate signaling pathways or directly regulate glycolytic enzymes to influence glucose metabolism in cancer cells. LncRNA H19 plays an important role in the occurrence of GC. Zhang et al observed that H19 was overexpressed in GC tissues compared with adjacent normal tissues. High H19 expression was associated with poor OS and can be regarded as an independent predictor of the OS of GC patients. It is also associated with lymph node metastasis and invasion in GC patients. H19 was involved in the aerobic glycolysis of tumor cells. Under hypoxic conditions, H19 could regulate PDK1 to influence the glycolysis process—PDK1 inhibits pyruvate dehydrogenase activity, thereby reducing pyruvate entry into the tricarboxylic acid cycle and shifting metabolism toward glycolysis.[27] In addition to regulating PDK1, H19 also modulates glycolysis by interacting with another key glycolytic enzyme PGK1. It produces the first ATP in the glycolytic pathway. It is also a biomarker for lung cancer, GC and breast cancer. PGK1 can promote GC proliferation by regulating the AKT/mTOR signaling pathway.[39] Due to the co-localization of PGK1 and H19 in the cytosol, Chen et al[27] found that low expression of H19 reduced the amounts of glucose and lactic acid consumed by GC cells. The level of H19 in GC cells was positively correlated with the levels of PGK1 mRNA and protein. It indicated that H19 provided new functions in regulating aerobic glycolysis and proliferation of GC. H19 affected aerobic glycolysis and cell proliferation in GC cells through the miR-19a-3p/PGK1 pathway.

Abhd11-As1

ABHD11-AS1 is a newly discovered type of lncRNA in recent years. It promotes the malignant progression of tumors such as thyroid tumors and ovarian cancer. Previous studies have shown that ABHD11-AS1 is significantly upregulated in the gastric tissues and gastric juices of GC patients.[63] It is also associated with the survival rate of GC and can be used to predict the

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prognosis of cancer. It has been reported that ABHD11-AS1 can synergize with miR-361-3p to regulate PDPK1 to promote GC cell proliferation and inhibit apoptosis.[63] The transcription factor c-Myc is involved in various cellular processes, including glucose metabolism processes, especially glycolysis.[64] In many types of cancers, c-Myc can directly transcriptionally activate glycolytic genes. This promotes glycolytic activity. It also increases glucose uptake and rapidly converts glucose into lactic acid. Subsequently, it leads to the proliferation, migration, and metastasis of cancer cells.[65] Feng[28] et al found that ABHD11-AS1 was highly expressed in GC cells. High expression of ABHD11-AS1 in GC cells can upregulate the expression level of c-Myc. By increasing the expression of c-Myc, it may recruit more downstream glycolytic target genes of c-Myc, such as GLUT1, HK2, ENO1, PKM2, and LDHA, thus promoting the aerobic glycolysis process and influencing the malignant progression of tumors. The study found that the expression level of ABHD11-AS1 in GC tissues was significantly higher than that in adjacent normal tissues. This indicates that ABHD11-AS1 may be a potential biomarker for GC.[40]

CircRNAs Regulating Glycolysis in GC

Circular RNA (circRNA) is a type of non-coding RNA that stably exists in exosomes. Its gene sequence is rich in multiple reaction elements of miRNAs. It can adsorb miRNAs and act as a sponge molecule for miRNAs to regulate the expression of target genes. Thus, a circRNA-miRNA-mRNA network is formed and participates in the occurrence and development processes of GC. CircRNA may also serve as a potential target for the targeted therapy of GC.[41] The circRNA-miRNA-mRNA network in exosomes participates in regulating the proliferation, migration, and invasion of GC. It induces the epithelial-mesenchymal transition, mediates the angiogenesis, regulates the metastasis, controls the chemoresistance and radiosensitivity of GC. The network plays an important role in the occurrence and development of GC.[42] Currently, there is already evidence indicating that circRNA plays an indispensable role in hepatocellular carcinoma, glioma, osteosarcoma, and GC.[43] Regulatory mechanism of circRNAs regulating glycolysis on GC are shown in Figure 2.

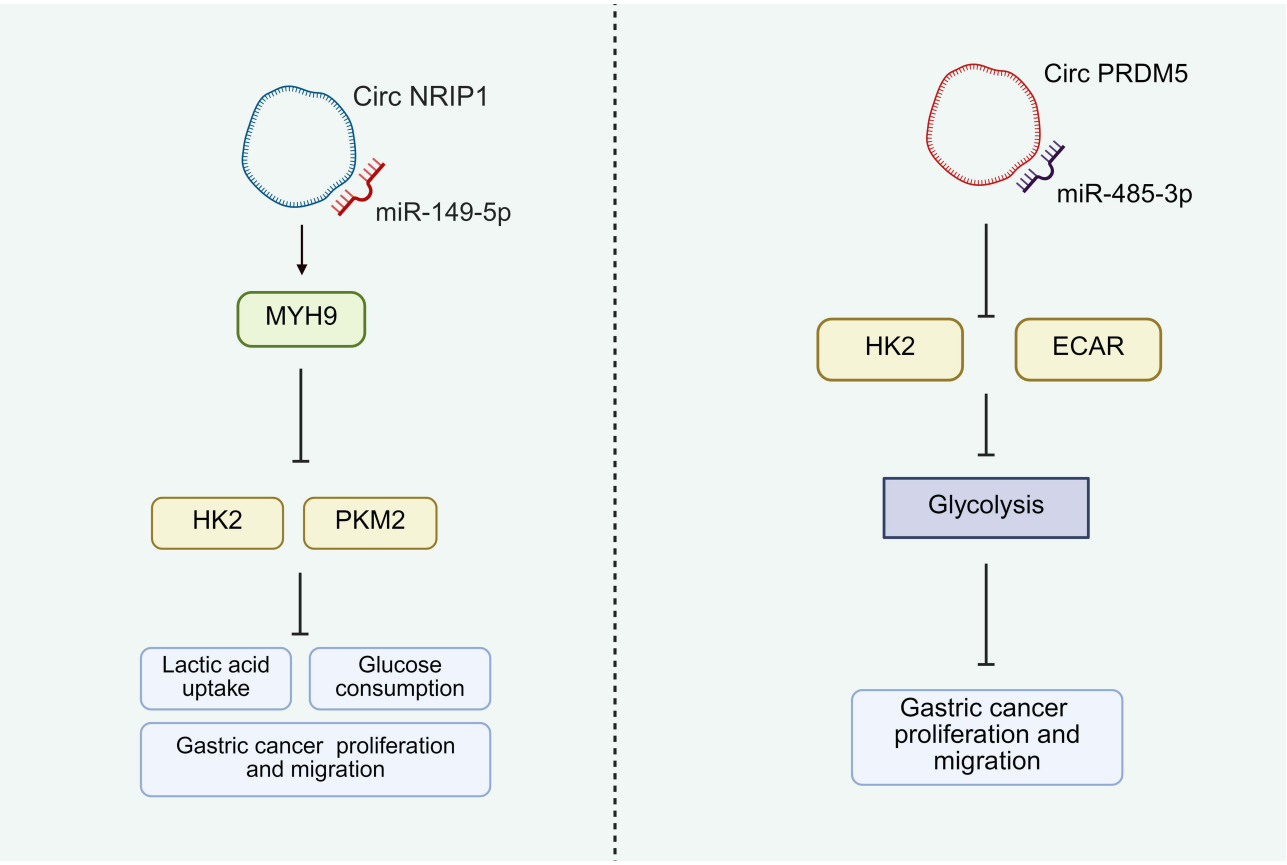

Figure 2 Regulatory mechanism of circRNAs regulating glycolysis on GC.

circNRIP1

CircNRIP1, derived from the NRIP gene and located on chromosome 21, is composed of the head-to-tail splicing of exon 2 and exon 3. Zhang et al[44] found that circNRIP1 was highly expressed in GC, which was positively correlated with tumor size and the stage of lymphatic invasion. The overall survival of patients with a high expression level of circNRIP1 was significantly shortened. In addition, Zhang et al also confirmed that circNRIP1 could adsorb miR-149-5p, further activate the AKT1/mTOR signaling pathway, and promote the proliferation, migration, and invasion of GC cells.[44] In addition, Xu et al[66] confirmed through in vitro experiments that circNRIP1 maintained HIF-1α-dependent glucose metabolism by adsorbing miR-138-5p. CircNRIP1 promoted glucose consumption by sponging miR-149-5p, which targets AKT1, thereby enhancing glycolysis and facilitating GC migration.[67] As a tumor suppressor, miR-186-5p is a downstream target miRNA of circNRIP1. MiR-186-5p regulate the biological functional effects of GC, including growth and metastasis, in a low-expression pattern. Liu et al[25] knocked out circNRIP1 to evaluate the biological functions. They found that the downregulation of circNRIP1 expression in GC cells inhibited cell proliferation, migration, and glycolysis. circ-NRIP1 interacts directly with miR-186-5p. Knockdown of miR-186-5p restored the effects of circ-NRIP1 silencing on proliferation, apoptosis, migration, and the contents and activities of glycolytic rate-limiting enzymes hexokinase 2 (HK2) and phosphofructokinase (PFKP).

circPRDM5

Circ_0005654 (also known as circPRDM5) is located on chr4. It is generated by the head-to-tail splicing of exons 8–14 of the PR/SET domain 5 (PRDM5) gene. Recent studies have demonstrated the high diagnostic value of circPRDM5 in distinguishing GC patients from healthy controls. The regulation of circRNA in biological processes is mainly attributed to sponging miRNAs. MiRNAs are a type of conserved small RNAs that function by cleaving mRNA molecules or inhibiting mRNA translation. An increasing number of miRNAs have been found to act as tumor suppressors or oncogenes to regulate the malignant phenotypes of GC, such as cell apoptosis, proliferation, angiogenesis, and metastasis.[45] MiR-485-3p is a miRNA that mediates cancer progression. Bioinformatics analysis shows that circPRDM5 contains the binding site of miR-485-3p.[46] CircPRDM5 inhibits the proliferation and motility of GC cells, reduces the expression of Ki67 and N-cadherin, and increases the expression of E-cadherin. The glycolytic pathway is accompanied by a change in cytosolic pH known as the extracellular acidification rate (ECAR) response. HK2 is a key regulatory enzyme in the process of cellular glycolysis. Glucose metabolism is evaluated by detecting the expression of HK2 and ECAR. Lan et al[26] found that circPRDM5 inhibited glycolysis by regulating the expression of HK2 and ECAR. It inhibited the progression of GC by reducing glucose metabolism. In addition, Lan et al[26] demonstrated that miR-485-3p overexpression in GC cells abolished the tumor-suppressive effects of circPRDM5, establishing the functional significance of the circPRDM5/miR-485-3p axis in GC progression.

MiRNAs Regulating Glycolysis in GC

miRNAs are a class of small ncRNAs. The regulation of gene expression is mainly manifested at the post-transcriptional level. miRNAs can regulate the degradation of mRNAs through complementary sequences, so that they can regulate the progression and metastasis of tumors.[47] In the advanced stages of GC, miRNAs can act as both activators and inhibitors of metastasis.[48] Regulatory mechanism of miRNAs regulating glycolysis on GC are shown in Figure 3.

rs61991156

Since glycolysis provides most of the energy required for cell proliferation, cancer cells need to activate glycolysis for proliferation even in the presence of oxygen.[29] Pyruvate kinase (PKM2), a key regulatory enzyme in the glycolysis process, is involved in the final step of glycolysis and is detected in most cancers.[68] PKM2 is regulated by miRNAs, which can be targeted and inhibited by miR-326, miR-122, miR-124, miR-137 and miR-379. Cao et al[23] found that rs61991156 in miR-379 is involved in the occurrence of GC by acting on the 3'UTR region of PKM2. There is a significant association between the rs61991156 gene and Hp infection, tumor size, degree of differentiation and metastasis. This indicates that rs61991156 is associated with the low glycolytic capacity of GC by enhancing the regulation of PKM2.

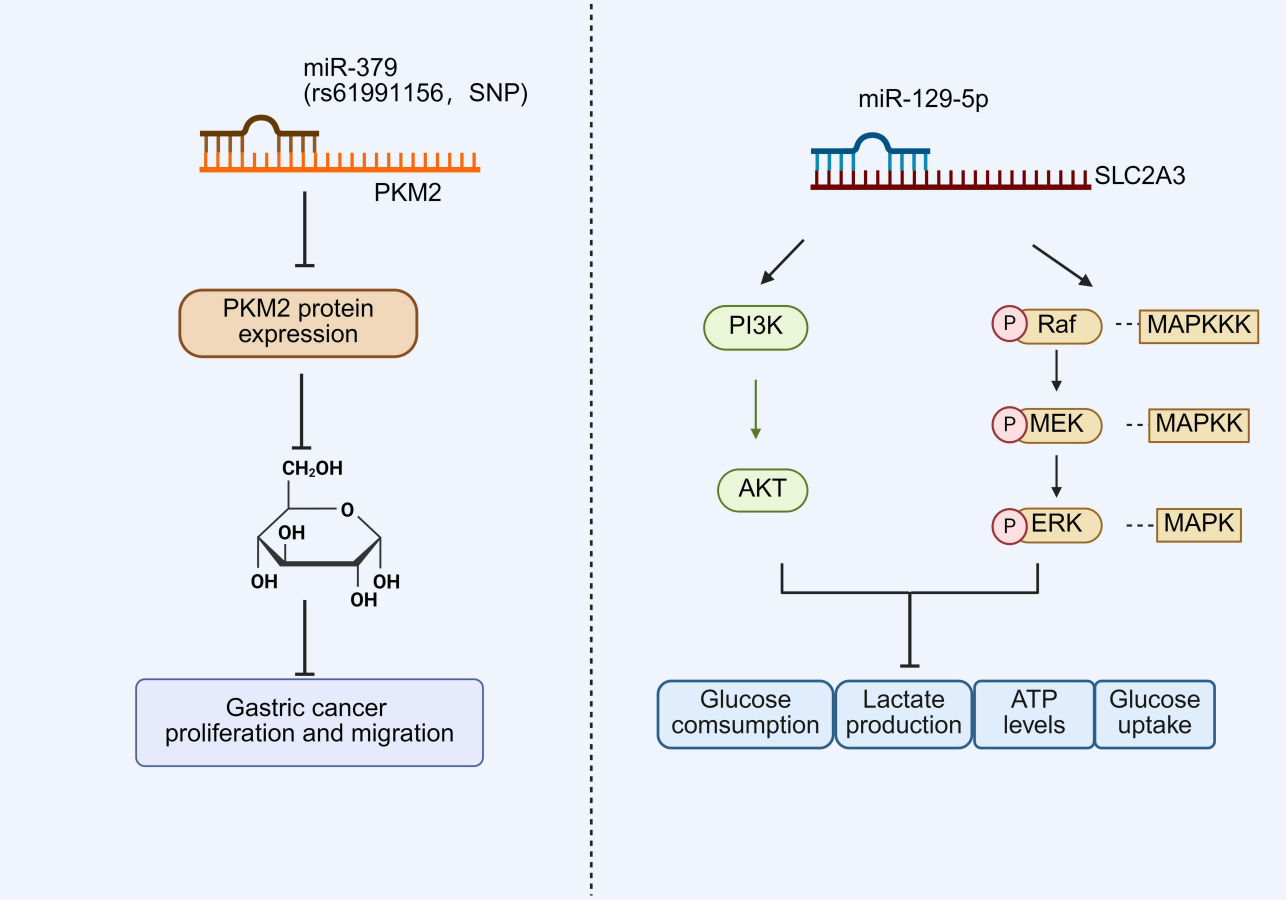

Figure 3 Regulatory mechanism of miRNAs regulating glycolysis on GC.

miR-129-5p

Tumor cells increase glucose consumption through aerobic glycolysis, which provides essential substances for tumor cell proliferation and migration. miRNAs interact with their target genes, which contributes to the metabolic reprogramming of cancer cells and plays a significant role in the pathogenesis of GC. Intermediates in glucose metabolism upregulate the facilitated glucose transporter (GLUT) protein for adequate glucose uptake.[69] The solute carrier family 2 (SLC2A), encoding GLUT proteins, is responsible for the first step of utilizing cellular glucose. While SLC2A1 (GLUT1) is the most ubiquitously expressed member and provides basal glucose uptake in many tissues and cancers, SLC2A3 (GLUT3) exhibits distinct properties. SLC2A3 is a transporter protein gene that has a high affinity for glucose. Positive staining results of SLC2A3 have been detected in several malignant tumor tissues, including those of GC.[70] The affinity of SLC2A3 for glucose is much higher than that of SLC2A1, enabling it to take up glucose more efficiently under low-glucose conditions in the tumor microenvironment. This provides a key advantage for the malignant proliferation of gastric cancer cells. MiR-129-5p has been identified as a candidate inhibitor of glucose metabolism and cell proliferation. SLC2A3 is the direct functional target gene of this miRNA in GC cells. The miR-129-5p/SLC2A3 axis can be a candidate therapeutic target for GC treatment. MiR-129-5p directly targets the 3′-UTR of SLC2A3, thereby inhibiting glucose consumption, lactate production, cellular ATP levels, and glucose uptake in GC cells. In addition, miR-129-5p interacts with SLC2 and participates in the PI3K-Akt and MAPK signaling pathways to regulate glucose metabolism and growth in GC. Furthermore, non-coding RNA-mediated glycolysis regulation in GC has also been discovered in recent studies.[71,72]

Enzymes Regulating Glycolysis in GC

Pyruvate Kinase M2

Pyruvate kinase (PK) is a key rate-limiting enzyme in glycolysis and determines the success of the glycolytic process. In mammals, there are mainly four subtypes of pyruvate kinase (PK), including PKM1, PKM2, PKL, and PKR. PKM2 exists in the form of a dimer or a tetramer in different tumor cells. In the process of glycolysis, PKM2 catalyzes phosphoenolpyruvate (PEP) to produce pyruvate and ATP for energy supply. Under anaerobic conditions, pyruvate is reduced to lactate by lactate dehydrogenase. After knocking down PKM2 in cancer cell lines using shRNA, an increase in glucose uptake and oxygen consumption as well as a decrease in lactate production were detected in the cells. These changes could be reversed after reintroducing PKM2, suggesting that PKM2 promotes cell proliferation and the formation of xenograft tumors.[49] PKM2 can also cause GC development by mediating the activation of the PI3K/Akt/mTOR signaling pathway. Feng et al[50] treated GC cells with the specific PI3K inhibitor LY294002 and found that it could inhibit the proliferation of GC cells, reduce cell viability and significantly increase the early apoptosis rate. After treating GC cells with different concentrations of LY294002 respectively, they found that the expressions of p-Akt, p-mTOR, HIF-1α, and PKM2 all decreased, and the degree of decrease was dose-dependent. Therefore, it is speculated that the PI3K/Akt/mTOR/PKM2 signaling pathway can promote the proliferation of GC cells and the aerobic glycolysis pathway.[51] So, blocking the key rate-limiting enzyme PKM2 in the glycolysis process may provide an effective approach to address the mechanism of GC development.

In addition, the non-metabolic functions of PKM2 include regulating gene transcription and participating in signaling pathways related to cell proliferation and survival. In particular, the nuclear translocation of PKM2 is related to transcriptional regulation, which is conducive to the Warburg effect and promotes the immune escape mechanism.[73] Recent studies have shown that hsa_circ_0008035 promotes the activity of PKM2 by facilitating nuclear localization and reducing the glycosylation level of PKM2 dependent on EXT1.[52] Therefore, hsa_circ_0008035 can promote immune escape through the EXT1/PKM2 axis, thereby promoting the progression of gastric cancer.

Targeting PKM2 has been a focus of anticancer drug discovery. A prominent strategy involves using small molecule activator, TEPP-46, which promotes the formation of the highly active tetrameric form of PKM2. This forces cancer cells to proceed with more oxidative glucose metabolism, thereby suppressing the Warburg effect, lactate production, and tumor growth in preclinical models.[53]

Phosphoglycerate Kinase

Phosphoglycerate kinase 1 (PGK1) is a key enzyme in the process of glycolysis and an essential enzyme for the survival of organisms. It catalyzes the conversion of 1,3-bisphosphoglycerate into 3-phosphoglycerate and releases ATP. The catalysis of PGK1 is also one of the only two processes that generate ATP during glycolysis. Glucose and glycogen are first converted into pyruvate through the glycolysis process in cell metabolism. Pyruvate, as an important energy source, plays a significant role in both normal cell metabolism and tumor cell metabolism. The glycolysis pathway has a remarkable relationship with the occurrence and development of tumors.[54] PGK is active in tumor cells and may act as a transcription factor during the migration of tumor cells.[55] Schneider et al[74] used positron emission tomography/magnetic resonance imaging to demonstrate that PGK1 is promoting the tumor progression and metastasis of GC in a tumor mouse model. PGK1 is involved in the metastasis of GC to the peritoneum as well as other metastatic dissemination pathways, and it has an impact on the growth and differentiation of GC tumor stem cells. Zieker et al[75] found that the enhanced expression of PGK1 and signaling targets (chemokine receptor 4 (CXCR4) and β-catenin) in GC cells promoted the occurrence of GC. Therefore, PGK1 may serve as a prognostic marker or a potential therapeutic target to prevent the spread of GC cells to the peritoneum. The involvement of PGK1 in GC metastasis may have important therapeutic potential. Wilson et al[56] showed that knocking out or inhibiting PGK1 could effectively control the development and growth of gastric-derived peritoneal metastasis. Once PGK1 translocates into the nucleus, it promotes DNA replication and cell proliferation, thus establishing the role of PGK1 in GC migration. While no specific PGK1 inhibitor has yet reached clinical application, its role in metastasis makes it a promising target. Drug discovery efforts are underway to develop small-molecule inhibitors against its ATP-generating catalytic site. Additionally, given its

extracellular role in promoting angiogenesis, an alternative strategy could involve using neutralizing monoclonal antibodies to block PGK1-triggered signaling in the tumor microenvironment.

Lactate Dehydrogenase

Lactate dehydrogenase (LDH), a class of NAD-dependent kinases, has three subunits, including LDHA, LDHB, and LDHC, which can form six tetrameric isoenzymes. Lactate dehydrogenase is a metalloprotein containing zinc ions and is one of the important enzyme systems in anaerobic glycolysis, gluconeogenesis and glycolysis. It can catalyze the reduction and oxidation reactions between propionate and lactate, and can also catalyze the related α-keto acids. As a key regulatory enzyme in glycolysis, LDH facilitates the oxidation of pyruvate to lactate while concurrently converting NADH to NAD+, thereby augmenting lactate production.[57] Previous studies have shown that LDHA is overexpressed in a series of cancers and the high expression of LDHA in GC is associated with a shorter OS.[58] Forkhead box M1 (FOXM1) is an oncogenic transcription factor. By transcriptionally regulating its downstream target genes and networking with other factors, it plays a crucial role in regulating cancer cell proliferation, angiogenesis, invasion, and metastasis. Koo et al[76] found that knocking down the expression of FOXM1 in GC cells reduces LDH activity, glucose utilization rate and lactate production. On the other hand, the overexpression of FOXM1 increases LDH activity, glucose utilization rate and lactate production by transcriptionally regulating the expression of LDHA. These findings establish that the elevated FOXM1-LDHA axis promotes the proliferation, migration, and invasion of GC cells, with LDHA playing a crucial role in mediating the function of FOXM1. Consistent with the importance of LDHA, independent studies have shown that LDHA is frequently upregulated in GC. Liu et al[59] demonstrated that inhibition of endogenously elevated LDHA using its specific inhibitor oxamate attenuates aerobic glycolysis, cell proliferation, and metastatic potential in GC cells. Rao et al[77] showed that LDH is an independent factor for predicting the prognosis of GC. Under the action of hypoxia-inducible factors, LDH can be activated and its expression is upregulated, which helps to provide a large amount of energy for tumor growth. More importantly, the lactic acid production driven by LDHA is at the core of the Warburg effect. The accumulation of lactic acid leads to the acidification of the tumor microenvironment. This acidic condition can not only directly inhibit the function of effector immune cells, but also help recruit inhibitory cells such as regulatory T cells, weakening the anti-tumor immune response.

Fructose-6-Phosphate-2-Kinase 3

Fructose-6-phosphate-2-kinase 3 (PFKFB3) is an important rate-limiting enzyme in the process of glycolysis. As an isoenzyme of phosphofructokinase (PFK-1), PFKFB3 is also involved in the glycolysis process of cells. It catalyzes the formation of fructose-1,6-bisphosphate from fructose-6-phosphate, thereby preventing the synthesis of sucrose and starch from fructose-6-phosphate, and plays a role in controlling the entire glycolysis process. PFKFB3 is also regulated by feedback from some metabolites, such as ATP, PEP, and citric acid. When the metabolites decrease and the phosphate groups increase, the activity of PFKFB3 is enhanced, accelerating the rate of glycolysis. Research reports indicated that the loss of PTEN and the activation of RAS and AKT in tumors could increase the activity of PFKFB3, the rate-limiting enzyme in glycolysis.[60] The increased activity of PFKFB3 helped tumor cells rapidly uptaked glucose for glycolysis, thus provided energy for the proliferation of tumor cells. Zhu W et al[78] found that the inhibition of PFKFB3 was able to induce cell cycle arrest, apoptosis and inhibition of invasion in GC cells. Results showed that PFKFB3 gene expression could be induced in malignant glioblastoma by activating the PI3K/AKT pathway.[79] Studies have confirmed that PFKFB3 regulates the growth of GC cells by influencing the phosphorylated PI3K/AKT signaling pathway.[80] Therefore, PFKFB3 may be a potential biomarker for GC. It is necessary to detect the expression of PFKFB3 in GC and analyze its value in the clinical prognosis of GC. In addition, some studies have also demonstrated the regulatory mechanisms of these enzymes and their clinical relevance in GC glycolysis.[81,82] Regulatory mechanism of enzymes regulating glycolysis on GC is shown in Figure 4.

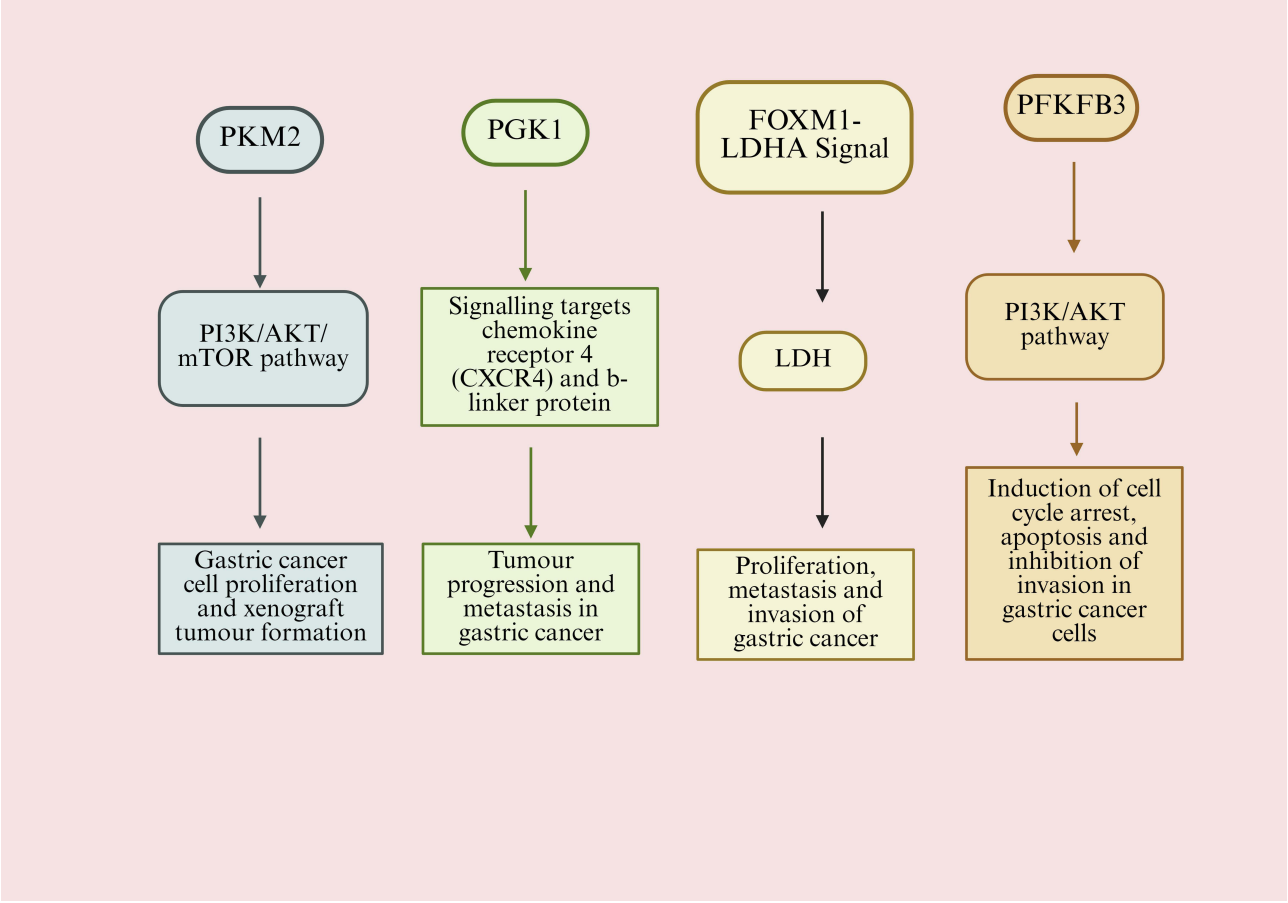

Figure 4 Regulatory mechanism of enzymes regulating glycolysis on GC.

Conclusion and Prospect

GC, as a common malignant tumor of the digestive system, has a complex pathogenesis that has not been fully elucidated. This review has synthesized current knowledge demonstrating that the abnormal activation of the glycolytic pathway is closely related to the occurrence, invasion and metastasis of GC. We have detailed the roles of key glycolysis-regulating enzymes and their upstream regulators in driving GC progression through various signaling pathways, highlighting their significant potential as therapeutic targets.

The glycolytic metabolic pathway plays a crucial role in cellular energy supply and biosynthesis. The intermediate products and ATP generated during the sugar metabolism process contribute to the proliferation, metastasis, and invasion of GC cells. Some genes related to non-coding RNAs in the glycolytic process are involved in regulating the occurrence of GC. The expression regulation of miRNA-related regulatory genes is mainly manifested at the post-transcriptional level, and it can regulate the proliferation and metastasis of GC cells by regulating the degradation of complementary sequences. CircRNA-related regulatory genes will target and regulate the expression of miRNA in the body and participate in the occurrence and development process of GC through metabolic signaling pathways. The lncRNA-related regulatory genes are highly expressed in tumor cells, which will promote important biological processes of tumors such as the cell cycle, apoptosis, angiogenesis, invasion and metastasis. In addition, some coding genes in the glycolytic process can also encode corresponding proteins to effectively regulate the occurrence, invasion and metastasis of GC. A range of experimental methods, including gene knockout, real-time quantitative PCR, Cell Counting Kit-8 (CCK-8) assay for assessing cell proliferation, Transwell assay, scratch assay, Western blotting, dual-luciferase reporter gene assay, and lactate content detection, are used to test the activity of GC tumor cells, further revealing the relationship between key glycolytic enzymes and the regulation of GC. However, current research still has limitations. There are significant

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differences between preclinical models and clinical samples. At present, most mechanism studies rely on gastric cancer cell lines cultured in vitro and xenograft tumor models, which cannot fully simulate the complex tumor microenvironment of tumors in the human body.

Preclinical studies have validated multiple lead compounds and delivery systems for these targets. However, clinical translation remains limited—only a few glycolysis inhibitors have entered early-phase trials. PFKFB3 inhibitor (AZ6738) are in Phase I trials for solid tumors to evaluate safety and efficacy, while LDHA inhibitor (GSK2837808A) are in preclinical GC models to test combination with chemotherapy.

Looking forward, translating these mechanistic insights into clinical practice is a paramount goal. While inhibitors for some targets like LDHA are under preclinical investigation, the discovery and development of specific, potent inhibitors for other key nodes like PKM2 and PGK1 remain critical future endeavors. A highly promising strategy lies in combination therapy. Integrating novel glycolytic inhibitors with conventional chemotherapy holds the potential to overcome chemoresistance. By disrupting the enhanced energy metabolism and biosynthetic pathways that fuel tumor growth and repair, glycolytic inhibitors could sensitize GC cells to cytotoxic drugs, thereby enhancing therapeutic efficacy and potentially improving patient prognosis. This approach may offer a complementary advantage to immunotherapy, particularly for patients with tumors that exhibit low immunogenicity but high glycolytic dependency. Future research must also prioritize the development of reliable biomarkers to identify patient subgroups most likely to benefit from metabolic interventions and the use of advanced models like patient-derived organoids to better predict clinical responses.

This study focuses specifically on elucidating the regulatory mechanisms of representative genes and enzymes involved in GC glycolysis, while other regulatory factors remain to be investigated. Future in-depth studies should focus on elucidating additional regulatory mechanisms within the glycolytic pathway. While exploring new mechanisms, efforts should also be made to develop and apply technical methods that can more truly reflect the metabolic state within tumors, to facilitate better clinical application and therapeutic development.

Abbreviations

GC, Gastric cancer; Hp, Helicobacter pylori; EBV, Epstein-Barr virus; HER2, Human epidermal growth factor receptor 2; MSI, Microsatellite instability; EMT, epithelial-mesenchymal transition; PKM2, M2-type pyruvate kinase 2; mTOR, Mammalian target of rapamycin; PI3K, Phosphatidylinositol 3-kinase; HIF-1α, Hypoxia-inducible factor 1 alpha; circRNA, Circular RNA; PK, Pyruvate kinase; PGK1, Phosphoglycerate kinase 1; LDH, Lactate dehydrogenase; PFKFB3, Fructose-6-phosphate-2-kinase 3.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts for interest in this study.

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