

Glucose metabolism in gastric cancer: The cutting-edge

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Abstract

Glucose metabolism in gastric cancer cells differs from that of normal epithelial cells. Upregulated aerobic glycolysis (Warburg effect) in gastric cancer meeting the demands of cell proliferation is associated with genetic mutations, epigenetic modification and proteomic alteration. Understanding the mechanisms of aerobic glycolysis may contribute to our knowledge of gastric carcinogenesis. Metabolomic studies offer novel, convenient and practical tools in the search for new biomarkers for early detection, diagnosis, prognosis, and chemosensitivity prediction of gastric cancer. Interfering with the process of glycolysis in cancer cells may provide a new and promising therapeutic strategy for gastric cancer. In this article, we present a brief review of recent studies of glucose metabolism in gastric cancer, with primary focus on the clinical applications of new biomarkers and their potential therapeutic role in gastric cancer.

Key words: Glucose metabolism; Warburg effect; Metabolomics; Gastric cancer; Biomarker; Therapy

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Core tip: Increased glucose consumption is a hallmark of cancer cells. Studies focusing on glucose metabolism provide a new perspective on gastric carcinogenesis and a novel approach to exploration of biomarkers and therapeutic targets in gastric cancer.

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and ranks second in cancer-related deaths^[1,2]. Recent advances in cancer diagnosis and treatment have resulted in limited improvement in gastric cancer-related mortality^[3]. Estimates even suggest that gastric cancer-related mortality will continue to increase^[4]. To improve the survival rate, several studies have elucidated molecular mechanisms of gastric cancer, and identified biomarkers predicting prognosis and response to treatment^[5,6]. A few biomarkers have been used as therapeutic targets for advanced gastric cancer^[7]. However, the therapeutic results are still unsatisfactory, which may be due to multiple genetic variations and changes in microenvironment, such as altered glucose metabolism promoting gastric carcinogenesis.

Several decades ago, alteration of glucose metabolism in cancer cells, termed "Warburg effect", was described. This discovery has revitalized the interest in the role of glucose metabolism in oncology since the widespread use of ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) to evaluate various types of malignant tumors^[8]. Compared with genomics and proteomics, metabolomics is a recent "omic" technique and the last step before phenotype, which provides new insight into pathophysiologic mechanisms in carcinogenesis. In fact, these biological pathways are not independent but co-dependent and co-operative in the progress of carcinogenesis.

The high mortality rate of gastric cancer is due to delayed diagnosis and lack of effective therapies for metastasis. Gastric cancer is generally screened using endoscopy and serum carbohydrate antigens, such as carcinoembryonic antigen (CEA). Clinical application of endoscopy is limited because of its relative invasiveness, cost and technical complexity, even in high-incidence countries of east Asia^[9]. Additionally, the current serum biomarkers have poor sensitivity and specificity for gastric cancer. Therefore, new biomarkers that are non-invasive and enable stratification of patients with high sensitivity and specificity for screening, diagnosis, prognosis, prediction, and monitoring of aggressive and advanced gastric cancer are needed. Metabolomics facilitates the investigation of these biomarkers *via* new and interesting analytical techniques that enable the detection of an array of metabolites in a single assay and open new avenues for diagnostics and drug discovery. By identifying and targeting the key link in altered glucose metabolism, specific and even individualized therapeutic strategies for gastric cancer may be developed.

This article will review the recent studies on glucose metabolism in gastric cancer and particularly the key applications of glucose metabolism in gastric cancer surveillance, diagnosis and therapy.

ALTERED GLUCOSE METABOLISM IN GASTRIC CANCER

In 1956, Otto Warburg initially observed that cancer cells generally undergo glycolysis instead of oxidative phosphorylation for energy, compared with non-neoplastic cells. The metabolic phenomenon is well known as aerobic glycolysis or the "Warburg effect"^[10]. Based on the results of "Warburg effect", increased glucose consumption, increased glycolytic activity and the accumulation of lactic acid are critical hallmarks of cancer cells^[11,12]. Compared with normal cells that mainly generate energy *via* mitochondrial oxidative phosphorylation, cancer cells predominantly obtain energy *via* increased glycolysis even under aerobic conditions. Converting glucose into lactate *via* glycolysis is inefficient in generating ATP, but it produces a large number of intermediate products driving cell proliferation. Therefore, increasing glucose consumption, leading to anaerobic glycolysis, is believed to provide an evolutionary advantage to cancer cells^[13]. The accumulation of lactic acid causes acidic microenvironment, and has a protective effect on tumor cells. Lactic acid induces the expression of glycolytic enzymes in tumor cells, such as 6-phosphofruktokinase1 (PFK1) to enhance the supply of ATP, and resist cellular apoptosis and promote metastasis^[14]. In addition, lactic acid promotes tumor angiogenesis, providing a suitable microenvironment for tumor development and metastasis.

A number of studies have confirmed the association between obesity and gastric cancer^[15-19]. An *et al.*^[20] confirmed the relationship between glucose metabolism, diabetes and gastric cancer by observing improved glucose metabolism after treatment of gastric cancer. A higher fasting serum glucose level significantly increased the incidence of gastric cancer in *Helicobacter pylori* (*H. pylori*)-seropositive patients nearly 3.5-4.2 fold^[21], suggesting that hyperglycemia may be an important cofactor in *H. pylori*-mediated gastric carcinogenesis^[22,23]. Song *et al.*^[24] used gas chromatography/mass spectrometry (GC/MS) to analyze the tissue metabolites of gastric cancer patients and healthy controls. The GC/MS revealed that several intermediate products of aerobic glycolytic pathways, such as fumaric acid and alpha-ketoglutaric acid increase significantly in cancer tissues than in the normal mucosa, suggesting that altered glucose metabolism may be an important parameter in distinguishing gastric cancer cells from normal cells. Similarly, abnormal glucose metabolism was observed by other researchers in gastric cancer tissue^[25-28].

Ikeda *et al.*^[29] demonstrated that the serum levels of 3-hydroxypropionic acid and pyruvic acid were upregulated in gastric cancer. Therefore, abnormal glucose metabolism may be related to tumor growth involving aggressive cancer cell proliferation, which requires a lot of energy, possibly causing altered

serum levels of a few intermediate metabolites. Serum metabolic profiling has a great potential role in identifying gastric cancer and the underlying metabolic mechanisms^[30].

Chen *et al.*^[31] used capillary electrophoresis-mass spectrometry based on moving reaction boundary (MRB-CE-MS) to investigate the metabolomics of gastric cancer patients' urinary samples to search for possible tumor biomarkers. They found that lactic acid was remarkably increased, while citric acid, malic acid, and succinate were significantly decreased in patients with gastric cancer compared with controls, suggesting that glycolysis is upregulated while tricarboxylic acid cycle is decreased in gastric cancer^[31]. The results implied that urinary metabolic profiles based on MRB-CE-MS analysis were useful in clinical diagnosis and prognosis of gastric cancer patients, consistent with findings from other studies^[32-36].

POTENTIAL MECHANISMS RESULTING IN ALTERED GLUCOSE METABOLISM IN GASTRIC CANCER

About 80 years after Warburg presented his hypothesis on aberrant glucose metabolism in cancer cells, his viewpoint has been confirmed using positron emission tomography (PET) with the glucose analog tracer in clinical oncology. The potential genetic, epigenetic and proteomic mechanisms underlying the relationship between glucose metabolism and cancer have only been partially elucidated.

Genes and alteration of glucose metabolism

Carcinogenesis is due to proto-oncogene activation and tumor suppressor gene inactivation, which are closely associated with glucose metabolism. As a proto-oncogene, Myc plays an important role in glucose metabolism by enhancing the expression of glycolytic enzymes including glucose transporter 1 (GLUT1)^[37], lactate dehydrogenase A (LDHA)^[38,39] and pyruvate Kinase M2 (PKM2)^[40]. Inactivation of p53, a well-known tumor suppressor, directly mediates the Warburg effect. In many cancers, p53 loss was observed to promote glucose flux *via* glycolytic pathway and reduced oxidative phosphorylation^[40]. The p53 protein increases oxidative phosphorylation and decreases glycolysis *via* downregulation of GLUT1, GLUT3, and GLUT4 expression^[41] and inactivation of glycolytic enzymes, such as phosphoglycerate mutase (PGM)^[42]. Recently, we studied the role of Klotho, an anti-oncogene, in gastric cancer and found that restoration of Klotho gene expression could remarkably inhibit cell proliferation and induce apoptosis in gastric cancer cells by downregulating the phosphorylation levels of IGF-1R, IRS-1, PI3K, Akt, and mTOR proteins. In the process, it may be associated with altered glucose metabolism, which requires further research^[43].

Enzymatic changes in glucose metabolism of cancer cells

The family of glucose transporters (Gluts), which control the glucose transport across the plasma into the cytosol, play a critical role in glucose metabolism^[44-46]. Increasing evidence shows that Gluts, especially the class I Gluts (1-4), play an key role in cancer glucose metabolism and cancer progression, such as in lung tumor^[47], breast cancer^[48], and bladder cancer^[49]. Recently, Shimada *et al.*^[50] reported that Glut-3 and Glut-1 expression were positive in benign gastric schwannoma with a high FDG uptake, but Glut-2 and Glut-4 expression were negative. 18F-FDG uptake in primary gastric lymphoma is also related to GLUT1 expression^[51]. Alakus *et al.*^[52] investigated GLUT-1 expression in 35 patients with gastric cancer, who underwent FDG-PET, and suggested that FDG uptake in gastric cancer is associated with GLUT-1 expression and that low FDG uptake in signet-ring cell carcinoma is due to the low expression of GLUT-1 in this histological subtype. Yamada *et al.*^[53] also observed that GLUT-1 expression occurred from an early cancer stage and was the most influential factor underlying the degree of FDG uptake in gastric carcinoma. FDG uptake correlated with GLUT-1 expression, responding to glucose metabolism, may serve as a prognostic biomarker of gastric cancer^[53]. However, the study of Takebayashi *et al.*^[54] showed no connection between FDG standardized uptake value (SUV) and GLUT-1 expression in gastric cancer. Currently, evidence on the role of Gluts in glucose metabolism in gastric cancer is still limited.

Several other glycolytic enzymes, including glucose-6-phosphate dehydrogenase (G6PD)^[55], hexokinase (HK)-II^[56,57] and pyruvate kinase M2 (PKM2)^[58,59], have been confirmed to participate in the carcinogenesis and predict the progression of gastric cancer. G6PD is involved in the normal processing of carbohydrates by converting glucose into ribose-5-phosphate, which is the first key step in glycolysis. Overexpression of G6PD in gastric cancer tissues is significantly correlated with progression of gastric cancer. Increasing G6PD levels in gastric cancer may enhance the level of NADPH which protects cells from DNA damage induced by reactive oxygen species (ROS)^[55]. Hexokinases catalyze the first phosphorylation step of glycolysis, to produce glucose-6-phosphate. HK-II is upregulated in many human cancers associated with enhanced aerobic glycolysis, the Warburg effect. HK-II was overexpressed in gastric cancer with worse prognosis^[57]. Unlike HK-I that is predominant in gastric polyps and normal mucosa, a significant elevation of HK-II was found in gastric cancer. Changes in the hexokinases isoenzymes composition in gastric mucosa with intestinal metaplasia were expressed to a lesser degree but with similar likelihood of cancer^[60]. HK-II, as a component of survival signaling nexus, integrates glucose metabolism and cell survival through Akt/mTOR pathways. It can positively regulate

glucose starvation-induced autophagy through TORC1 inhibition^[61]. Pyruvate kinase M2 (PKM2) is another glycolytic enzyme, which controls the final rate-limiting step of glycolysis by catalyzing the dephosphorylation of phosphoenolpyruvate (PEP) to pyruvate and is overexpressed in many human cancers^[62]. Recent studies have indicated that PKM2 was overexpressed in gastric cancer and associated with tumor size, depth of invasion and lymph node metastasis^[59,63]. The knockdown of PKM2 partially affected the stability of NF- κ B subunit p65 in gastric cancer cells, suggesting that post-translational regulation of p65 by PKM2 may be a plausible mechanism correlated with cell proliferation^[64]. Another study demonstrated that the PKM2 expression, E-cadherin expression, and ERK1/2 phosphorylation were correlated with each other in gastric cancer cells, which suggested an important connection between PKM2 and E-cadherin in the motility and invasion of gastric cancer cell stimulated by EGFR^[65].

Signaling pathways involved in glycolysis

Hypoxia-inducible factor pathway: One of the common explanations for enhanced glycolysis in cancer cells is cancer tissue hypoxia, attributed to the rapid growth of cancer cells^[66]. Hypoxia is now recognized as a key factor in carcinogenesis, and Hypoxia-inducible factor (HIF)-1 is a critical transcription factor of the HIF pathway involved in both sensing and responding to changes in cellular oxygen, which aids in the survival of cells in hypoxic microenvironment^[67,68]. Increasing evidence shows that HIF-1 and HIF pathway may mediate gastric carcinogenesis. Generally HIF-1 is not or minimally expressed in the normal gastric mucosa from patients with gastric cancer, peptic ulcer or dyspepsia^[69,70]. Recently, Lin *et al.*^[71] conducted a systematic review of the literature and meta-analysis to investigate the role of HIF-1 α in gastric cancer. Of the nine studies including 1103 subjects, HIF-1 α positive expression was observed in half the patients and always indicated poor prognosis for patients with gastric cancer. Activation of the Ras-MAPK signal transduction pathway and PI3K-AKT-mTOR signaling, and loss of tumor suppressor proteins, such as PTEN and p53, elevated HIF-1 α expression. HIF-1 α directly stimulates glycolysis by activating the expression of glucose transporters and several key glycolytic enzymes, such as HK, PKM2 and LDH-A. The HIF-1 α -dependent pathway increases glycolysis and inhibits mitochondrial O₂ consumption, then promoting tumor cell survival^[72,73].

Insulin signaling pathway: Another important signaling pathway involved in glucose metabolism is insulin signaling pathway. Suppressing glucose production in the liver and enhancing glucose uptake in the insulin-sensitive tissues of the human body is well known as the classic action of insulin mediating

glucose homeostasis. Insulin is also implicated in cellular activation and angiogenesis mediated by the activation of signaling of the insulin receptor (IR), insulin growth factor (IGF)-1, IGF2 and the IGF-1R^[74,75]. Increased IGF signaling is associated with many cancers^[74-76]. In addition, downregulation of the IGF-1 receptor expression and reduced signaling have been found to inhibit tumor growth^[77]. Increasing IGF-I expression was observed in gastric tumors progressing from benign proliferative lesions to malignant lesions^[78]. IGF-I can induce epithelial-to-mesenchymal transition (EMT) which is involved in the metastasis of numerous cancers, by activating a PI3K/Akt-GSK-3 β -ZEB2 signaling pathway in gastric cancer BGC-823 cells^[79]. Li *et al.*^[76] and Min *et al.*^[80] found that IGF-IR signaling promoted tumor growth in gastric cancer. IGF-1R blockade reduced gastric tumor growth *in vivo* and *in vitro* by inhibiting both angiogenesis and lymphangiogenesis, attributed to the decreasing activity of both protein kinase B (Akt) and mitogen-activated protein kinase (MAPK). IGF-1R expression in gastric cancer was correlated with lymph node metastasis, poor prognosis and high histological malignancy grade, and may play an important role in tumor growth and metastasis *via* the lymphatic pathway^[81].

PI3K-Akt-mTOR pathway: The PI3K-Akt-mTOR pathway is currently a widely studied intracellular signaling pathway. It is directly associated with cellular quiescence, proliferation, cancer, and longevity. Recent studies showed that the PI3K-Akt-mTOR pathway was activated in gastric cancer and activation of the pathway was correlated with metastasis, poor prognosis and lower survival in gastric cancer^[82,83]. In addition, activation of this pathway promoted glycolysis and inhibited autophagy^[84]. Akt expression directly increases the surface translocation of glucose transporters and enhances aerobic glycolysis by prompting HK- II binding to voltage-dependent anion channel. (VDAC) at the outer mitochondrial membrane^[85]. PI3K/Akt also increased fatty acid synthesis in cancer cells by suppressing mitochondrial acid fatty oxidation and promoting a metabolic phenotype supporting cancer cell growth and proliferation in the absence of glucose by oxidizing fatty acid^[86]. Upregulation of the PI3K-Akt-mTOR pathway and increased glucose consumption *via* glycolysis offer evolutionary advantages to cancer cells in normoxia as well as hypoxia.

In general, the regulation of glucose metabolism in carcinogenesis is a multi-factor, multi-step process. In their review, Smolková *et al.*^[87] presented the wave hypothesis of metabolic regulation during carcinogenesis, which consisted of four waves. First, the fundamental reprogramming of gene expression or initiation by stem cells establishes the conditions conducive to cancer cell proliferation. Second, subsequent responses to microenvironmental conditions cause a typical Warburg

effect. Third, aglycemia and nutrient shortage due to rapid cell growth during malignancy, stimulate glutaminolysis, which may influence restoration of suppressed mitochondrial biogenesis, leading to oxidative phosphorylation (OXPHOS)-dependent cancer cells. The fourth wave of gene reprogramming entails retrograde signaling from revitalized mitochondria.

CLINICAL APPLICATION OF ALTERED GLUCOSE METABOLISM IN GASTRIC CANCER

Role of glucose metabolism in gastric cancer imaging

Based on the increased glucose uptake in cancer cells, PET/CT scan can reflect cancer cell glucose metabolism using ^{18}F -2-fluoro-2-deoxy-D-glucose (^{18}F -FDG) as a tracer and has been widely used in the diagnosis and monitoring of human cancers. ^{18}F -FDG is the most commonly used radiolabeled glucose analog in clinical practice. Currently, gastroscopic biopsy and histopathological examination are the gold standard of diagnosis of gastric cancer. In recent years, PET/CT, integrating images from FDG-PET with CT, have been used to detect gastric cancer. Compared with contrast-enhanced CT (CECT) and endoscopic ultrasonography, PET/CT does not offer the advantages of sensitivity and accuracy, and therefore, FDG-PET/CT scans are not indicated in routine staging of gastric cancer^[88]. Nevertheless, due to its high specificity, PET/CT is useful when CECT findings were equivocal and in the detection of distant lymph node metastasis^[89].

Several factors influence the visibility of PET/CT in gastric carcinoma. PET/CT imaging is based on increased glucose metabolism in gastric cancer. FDG avidity depends on tumor histologic subtype. Low FDG uptake is more often seen in diffuse type histology (mucinous, signet ring and poorly differentiated) compared with the intestinal subtype, which depends on GLUT-1 expression. The low GLUT-1 expression may lead to low FDG uptake in signet-ring cell carcinoma of gastric cancer^[52,53]. The maximum standardized uptake value [SUV(max)] of PET/CT is significantly correlated with tumor size, and lower FDG uptake is often found in early gastric carcinoma which is likely due to less total cancer cells in the primary lesions^[53,54]. The motility and physiological uptake of ^{18}F -FDG in the stomach also influence the accuracy of PET/CT in diagnosis of gastric cancer. Stomach distension to increase gastric volume with water or milk can reduce physiological gastric FDG uptake, display the lesions more clearly and significantly improve the diagnostic accuracy^[90,91].

Although PET/CT is not recommended in the primary detection of gastric cancer due to its poor sensitivity, FDG-PET shows better results in the evaluation of biological aggressiveness and/or patient prognosis in gastric cancer^[92,93]. ^{18}F -FDG uptake is an independent and significant prognostic indicator of

tumor recurrence in gastric cancer. Lee *et al.*^[92] also investigated the role of ^{18}F -FDG PET in gastric cancer prognosis based on histopathological subtypes and found that patients with negative ^{18}F -FDG tumor uptake showed better recurrence-free survival than those with positive ^{18}F -FDG tumor uptake in the subgroup of patients with gastric adenocarcinoma, while the opposite findings were obtained in the subgroup patients with signet-ring cell carcinoma and mucinous adenocarcinoma.

A higher SUVmax of ^{18}F -FDG PET/CT was linked to the presence of microsatellite instability (MSI) in gastric cancer^[94]. Gastric cancers with MSI tend to show less lymph node metastasis and manifest favorable prognosis^[95]. The high SUVmax of ^{18}F -FDG PET/CT showed poor prognosis in gastric cancer. The SUVmax more than 3.8 indicated increasingly aggressive behavior, elevated postoperative recurrence and shorter relapse-free survival in gastric signet-ring cell carcinoma^[96]. The degree of ^{18}F -FDG uptake in gastric cancer predicts histologically positive lymph nodes and non-curative surgery. The sensitivity, specificity and accuracy of the diagnosis of metastatic lymph node were 73.5%, 74.5% and 74.1%, respectively, using the SUVmax cutoff of 3.75 or greater. When the SUVmax was defined as 4.35 or more for metastatic lymph nodes to predict non-curative surgery, the sensitivity and specificity were 58.8% and 91.6%, respectively, which were higher than those obtained with CT scan. Therefore, pretreatment PET/CT may be helpful in optimizing surgical strategy^[96].

Postoperative routine follow-up of gastric cancer is important to the surveillance of recurrence. The conventional follow-up using computed tomography (CT) and endoscopy, cannot frequently detect recurrence before symptom development. PET/CT shows good specificity for asymptomatic advanced gastric cancer and provides useful information for the clinical management of patients with suspected gastric cancer recurrence^[97]. However, prudence should be exercised with the incidental findings of PET/CT, most of which were benign with additional investigations associated with high cost^[98].

Despite adequate surgery with radical lymphadenectomy, the prognosis of advanced gastric cancer is still poor. Since the early 1990s, neoadjuvant therapy gained importance for the treatment of locally advanced or initially unresectable GC^[99]. Currently, measurement of changes in morphology using different imaging modalities is still the main approach to evaluate the response to neoadjuvant therapy. However, alterations in glucose metabolism always precede changes in morphological changes. The response to neoadjuvant therapy initially manifests in altered glucose uptake, demonstrated with ^{18}F -FDG PET. In fact, a dual modality PET-CT has been recommended for early assessment of therapeutic response in GIST patients treated with imatinib^[100]. In gastric cancer, changes in FDP uptake occur early during the course of neoadjuvant therapy,

which is significantly related with histopathological responses, and a complete metabolic response in FDP-PET always suggest favorable prognosis^[101]. It is still a challenge to distinguish the complete histopathological remission after neoadjuvant therapy by PET/CT. Different histologic subtypes may interfere with the evaluation of PET/CT and the best time to undergo post-treatment PET/CT is still unclear.

PET/CT is a powerful, noninvasive metabolic imaging modality for detecting many human tumors. However, detection of gastric cancer by PET/CT may seem less than ideal, because FDP uptake is strongly related to tumor size and histopathological subtype^[102]. In order to improve the sensitivity and specificity of PET/CT in evaluating gastric cancer, other tracers target more specific biological processes, such as proliferation (¹⁸F-3'-fluoro-3'-deoxy-L-thymidine; ¹⁸F-FLT), tumor hypoxia (¹⁸F-fluoromisonidazol; ¹⁸F-FMISO) and phospholipid metabolism (radioactively labeled choline derivatives)^[103-105]. ¹⁸F-FLT, as a substrate for thymidine kinase 1, is a new PET tracer with the potential ability to accumulate in proliferating tissues and malignant tumors^[106]. A higher accumulation of ¹⁸F-FLT was reported in gastric cancer than in normal gastric mucosa. ¹⁸F-FLT uptake is significantly correlated with gastric cancer differentiation and cellular density^[107]. ¹⁸F-FLT PET was more sensitive than ¹⁸F-FDG PET in imaging gastric cancer, especially in tumors frequently presenting with or without low ¹⁸F-FDG uptake, and may improve early evaluation of response to neoadjuvant treatment^[103]. However, F-FLT PET/CT imaging is not recommended for pre-treatment assessment of metastatic gastric cancer as it does not show significant advantages in evaluating liver and bone metastases, compared with ¹⁸F-FDG PET/CT imaging^[108].

Role of glucose metabolites in gastric cancer screening and diagnosis

Currently, gastroscopy still represents the gold standard for diagnosis of gastric cancer. Despite its uncomfortable and invasive features, gastroscopy is widely used in the surveillance, early screening and follow-up of gastric cancer. Over the past few years, several tumor serum biomarkers have been used as novel non-invasive tools for early diagnosis of gastric cancer. However, due to low specificity and sensitivity, current serum biomarkers such as CEA and carbohydrate antigens are not as effective as other screening methods.

Recently, serum and urine metabolomic studies of gastric cancer based on the use of highly sensitive detection techniques may present a novel opportunity to seek potential new biomarkers for early screening of asymptomatic gastric cancer and its follow-up. Metabolomics is defined as a quantitative description of all endogenous low-molecular-weight components (< 1 kDa) in a biological sample, such as tissue, urine

or plasma, and aims to diagnose various diseases by analyzing the data^[109]. The small molecule endogenous metabolites are mainly composed of the intermediate products produced by the four metabolic cycles, which include the glucose metabolism, lipid metabolism, amino acid metabolism and nucleic acid metabolism, in which glucose metabolism is the core (Figure 1)^[110]. The intermediate metabolites are important in biological systems and are promising candidates for understand disease phenotypes^[111]. Metabolomic studies, comparing the metabolite profiles of cancer cells vs normal cells, offer an opportunity to identify the changes in metabolic pathways, which prompt carcinogenesis. Compared with genomics, transcriptomics and proteomics, metabolomics provides terminal molecular data of the biological system which may be an effective way to elucidate the phenotypic changes associated with cancer. Recently, metabolomic studies have been successfully conducted in gastric cancer^[24-36] and other human cancers^[112-115].

Metabolomics approaches in gastric cancer may be applied largely in three ways. First, specific metabolites responsible for phenotypes associated with cancer-related mutations should be identified. Second, the common metabolites with altered levels in gastric cancer cells compared with normal cells, need to be found. Third, the response of cancer metabolism to environmental changes needs investigation^[28,29]. Advances in the highly sensitive metabolomic methods and data analysis techniques may facilitate such applications in a single study^[116]. Metabolomic profiles may offer a chance to identify the potential biomarkers for early diagnosis, prognosis, drug target identification and treatment response. Recently, several metabolites were suggested as diagnostic and prognostic biomarkers for gastric cancer^[117,118]. Gastric carcinogenesis is a complex phenomenon involving multiple epigenetic and genetic factors including several genetic, environmental and infectious agents causing a cumulative effect in the early stages. The model of gastric carcinogenesis is well known and includes the following sequential stages: chronic atrophic gastritis (CAG), intestinal metaplasia (IM), gastric dysplasia (DYS) and finally gastric cancer (GC). Plasma metabolomic studies, in which fifteen identified metabolites were quantitatively detected, showed unique metabolic profiles in the different stages of GC. The metabolic phenotype of chronic superficial gastritis (CSG) is significantly different from CAG, IM, DYS and GC, whose plots clustered closely. A similar metabolic pattern was shown in IM and GC^[119]. The discriminative metabolites characterizing the different stages of GC may be widely used in gastric cancer screening and early diagnosis combined with endoscopy. As previously mentioned, several serum metabolomic studies in GC suggested significant metabolic differences between cancer and control groups, suggesting potential biomarkers for the early diagnosis of GC.

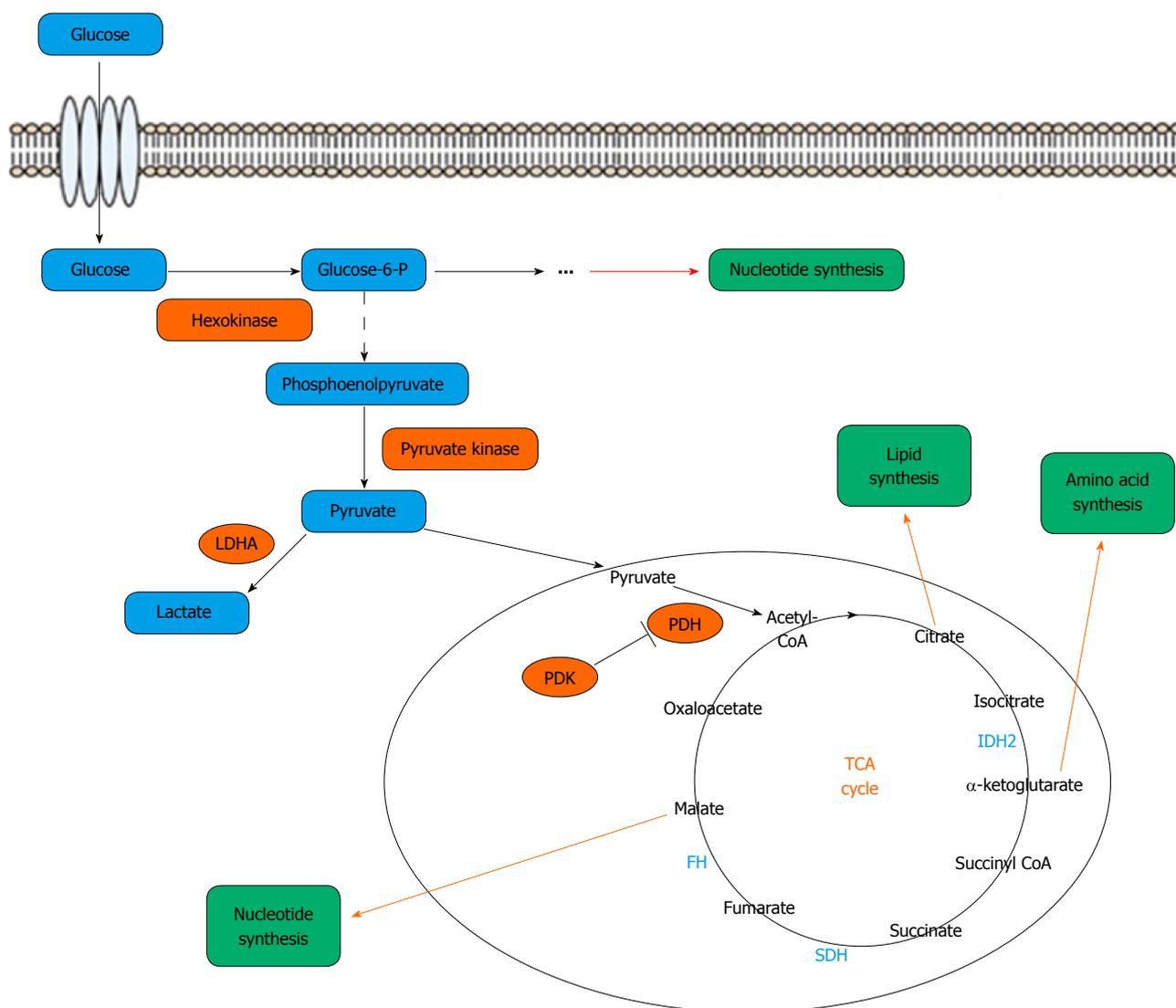


Figure 1 Glucose metabolism in gastric cancer. The figure incorporates the interplay between glucose and the other three metabolic pathways^[110].

Kim *et al.*^[33] studied urinary metabolomic biomarkers of gastric cancer in mouse models and found the presence of significant endogenous metabolic differences between tumor-bearing mice and controls. The study indicated that trimethylamine oxide (TMAO), 3-indoxylsulfate, hippurate, and citrate might serve as useful urinary biomarkers for the detection of gastric cancer in a mouse model. Jung *et al.*^[35] demonstrated that metabolomic changes in amino acid and lipid metabolism of urine samples resembled those in gastric cancer tissue, and were highly accurate in predicting gastric cancer with a much higher sensitivity than carbohydrate antigen 19-9 and CEA. Further, 4-hydroxyphenylacetate, alanine, phenylacetyl-glycine, mannitol, glycolate, and arginine levels were significantly related to T stage of gastric cancer. Compared with serum and urine samples, tissue samples require invasive approaches such as endoscopy and surgery, which limits their application in the screening and early diagnosis of gastric cancer. However, identification of new biomarkers

simultaneously in tissue and serum or urine samples is helpful. Tissue metabolic markers in gastric cancer were identified by some studies^[23,24]. Integrated the recent studies on the profiling of glucose metabolites in gastric cancer, lactate and fumarate were recognized as the most commonly biomarkers for gastric cancer screening and diagnosis^[120].

Role of glucose metabolites in gastric cancer prognosis

Recent advances in metabolomics have offered new avenues to predict gastric cancer metastasis. Hur *et al.*^[28] analyzed the levels of Krebs cycle components in gastric cancer tissues and found that the levels of pyruvic acid, lactic acid and ketone bodies were associated with histopathology. In particular, the levels of ketone bodies were significantly higher in cancer tissues with differentiated tumors than in undifferentiated tumors. Wu *et al.*^[25] found that the levels of phenanthrenol and butanoic acid were significantly decreased in invasive cancers (T3/T4) compared with non-invasive cancers (T1/T2). Compared with

glucose metabolites, amino acid and lipid metabolites seem to be more potential in predicting gastric cancer prognosis. Using animal models of human gastric cancer, Chen *et al.*^[121] demonstrated that proline and serine metabolism play an important role in metastasis, and may be used in predicting gastric cancer metastasis and progression. Further, Hu *et al.*^[34] investigated urinary metabolite profiling to identify possible biomarkers in gastric cancer metastasis. They found that the levels of alanine, glycerol and L-proline were lower and the level of myo-inositol was higher in the metastasis group. These urinary metabolites may be a potential prognostic biomarker for gastric cancer metastasis.

Role of glucose metabolism in gastric cancer therapy

Predicting drug response: Currently, chemotherapy has become a first-line therapy for advanced gastric cancer. However, chemotherapy is not the gold standard due to its lower effectiveness compared with its role in colorectal and breast cancers. Chemoresistance is a major challenge. Recent studies suggested that metabolomics may play an important role in investigating cellular responses to chemotherapy of cancer^[122-126]. Morvan *et al.*^[124] investigated metabolic changes associated with tumor response to chloroethyl nitrosourea (CENU), an anticancer agent, in two tumor models *in vivo* and observed the activation of metabolic pathways of DNA repair and adaptation to treatment. Metabolomics of tumor response to anticancer agents may enable identification of metabolic pathways of drug efficacy and evaluate the effectiveness of treatment. Wang *et al.*^[125] assessed metabolomic prediction of chemosensitivity in a human xenograft model of gastric cancer and determined that a series of endogenous metabolites, including 1-acyl-lysophosphatidylcholines, polyunsaturated fatty acids and their derivatives, were predictive of chemosensitivity in gastric cancer. Sasada *et al.*^[126] conducted a similar metabolomic analysis to investigate the intracellular response of human gastric cancer cells to 5-fluorouracil (5-FU), and showed a dramatic alteration in the number of metabolites, especially proline, glutamate and proline dehydrogenase (PRODH), in non-5-FU-resistant cancer cells during short-term treatment with 5-FU. However, the proline and glutamate levels and PRODH mRNA expression were less affected in 5-FU-resistant cancer cells. In the future, metabolic biomarkers may play an important role in evaluating treatment response to anticancer drugs.

Targeting glucose metabolism in gastric cancer therapy

Enhanced glucose metabolism *via* aerobic glycolysis followed by lactic acid fermentation plays a predominant role in rapid energy (ATP) synthesis. However, generation of large number of metabolites contributes to an acidic micro-environment conducive to cancer proliferation. Therapeutically targeting cancer cell

metabolism such as glucose metabolism is more convenient and associated with fewer side effects compared with the other biologic systems since cellular metabolic pathways represent the terminus of systems biology and control the other systems genetically.

Ketogenic diets consist of high fat, with moderate-to-low protein content, and very low carbohydrates. It reduced tumor growth and improved survival in a mouse model of malignant gastric cancer^[127]. Furthermore, ketogenic diets have been suggested to increase the effects of radiochemotherapy in non-small cell lung cancer xenograft models^[128]. Recent studies revealed that ketogenic diets act as adjuvant cancer therapy *via* mechanisms that increased oxidative stress and inhibited glucose metabolism *via* lipid metabolism.

Metformin, a first-line anti-diabetic drug, inhibited proliferation and induced apoptosis in cancer cells. Metformin decreased mitochondrial respiration chain activity and ATP production and induced the activation of LKB1-AMPK, causing the inhibition of Raptor-mTOR complex^[129,130]. High glucose concentrations reduced the effectiveness of metformin on cancer cell proliferation and failure to maintain glucose homeostasis may promote aggressive breast cancer phenotype^[129].

Tanshinone II A, a diterpene quinone extracted from the plant Danshen, has been recently reported as an effective adjunctive reagent in the treatment of gastric cancer^[131]. Lin *et al.*^[132] confirmed that TIIA treatment inhibited cell growth and the proliferation of gastric cancer by suppressing glucose metabolism in cancer cells. Another study conducted by Bhattacharya *et al.*^[133] revealed that hypoglycemia and enhanced glycolysis increased resistance to chemotherapy in gastric cancer.

Another very promising strategy is to design gastric cancer-specific and even individualized inhibitors of all the steps of the glycolytic pathway *via* metabolomics studies. Granchi *et al.*^[134] reviewed recent advances of new bioactive molecules which disturb cancer glycolysis. Different kinds of small molecules that inhibit all the steps of the glycolytic pathway have been identified, such as hexokinase II (HK II), 2-deoxy-D-glucose and 3-bromopyruvate (3-BrPA), which were accepted as cancer therapeutic targets in several studies. Similar potential and promising therapy for gastric cancer was described by Ngo *et al.*^[135] (Figure 2). Hexokinase II is a key factor catalyzing the first step of glycolysis, which consists of the transfer of glucose to glucose-6-phosphate^[136]. HKII is accepted as a very potential and attractive anticancer target. 2-deoxy-D-glucose, a glucose analogue, binds and inhibits HK II, resulting in cellular ATP depletion, cell cycle suppression and cell death^[137]. 3-BrPA, an alkylating agent and glycolysis inhibitor and designated as an orphan drug by FDA for liver cancer, has been identified to hinder glucose metabolism by inhibiting HK II^[138]. In addition, 3-BrPA inactivated the

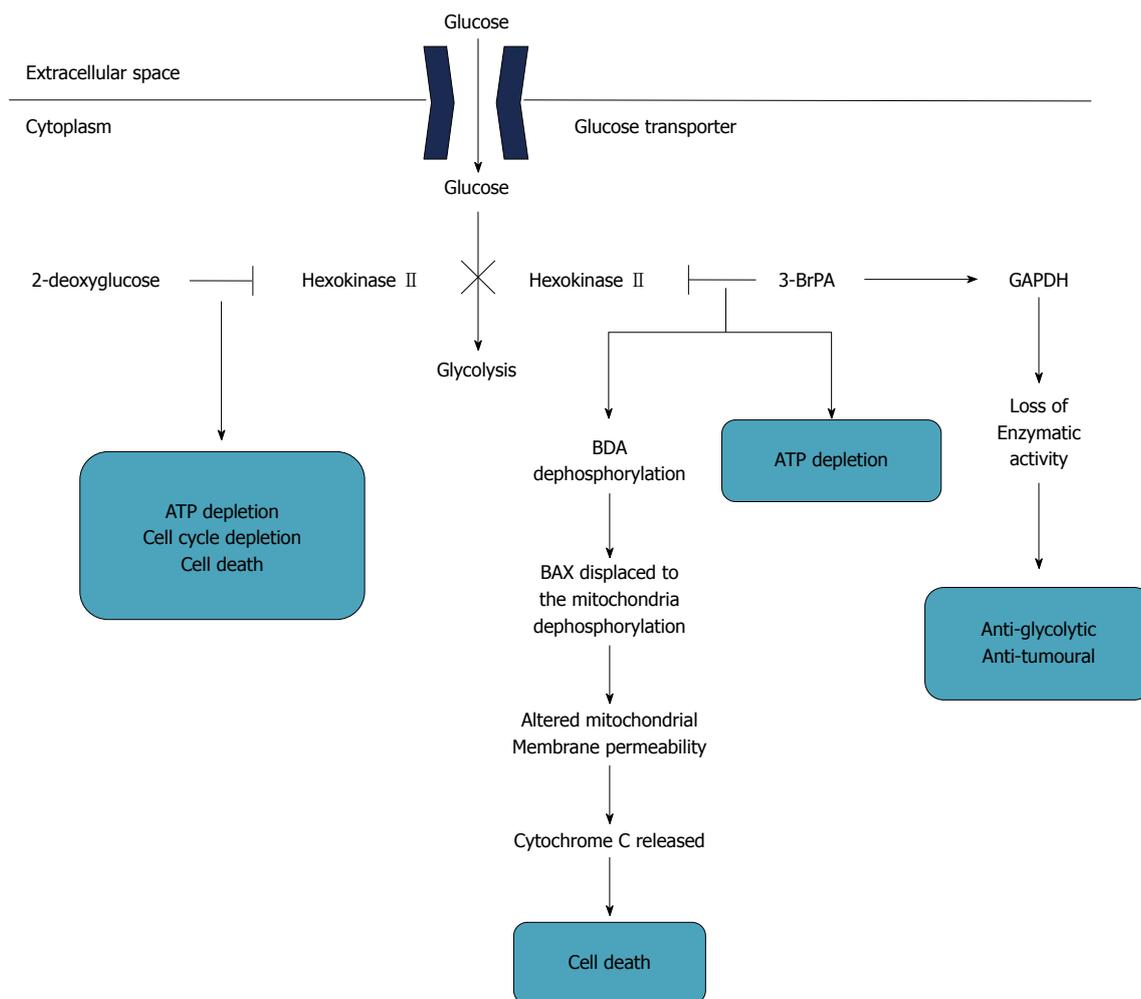


Figure 2 Targeting hexokinase II as a potential mechanism to inhibit the Warburg effect in cancer cells^[141].

glyceraldehydes-3-phosphate dehydrogenase (GAPDH) by GAPDH pyruvylation, leading to anti-glycolytic and antitumoral effects and mediating cancer cell death^[139].

Generally, most of the current glycolytic inhibitors showed only moderate efficacy when used as single agents, but in some cases demonstrated high potential when combined with other therapies. Currently, few therapeutic studies target gastric cancer metabolism. It is anticipated that further research will investigate the role of cancer-specific glycolytic inhibitors to develop effective therapeutic regimens for gastric cancer.

CONCLUSION

Altered glucose metabolism is a hallmark of gastric cancer, which provides new insights into gastric carcinogenesis and identification of biomarkers targeting specific metabolic aspects of gastric cancer. However, several hurdles remain before altered glucose metabolism is clinically used in the diagnosis and treatment of gastric cancer. The use of ¹⁸F-FDG PET is an exception. However, a major clinical application of metabolomics requires creation of spectral databases of metabolites of the normal population, similar to the

cancer genomic and proteomic databases. Further, the metabolites consist of a large group of small-molecule intermediates, which are too large for analysis using currently available technology. Another challenge is related to identification of cancer-specific biomarkers for gastric cancer, since metabolites may be considered as potential biomarkers for a range of cancers. It is anticipated that further research will focus on these aspects and promote the clinical application of glucose metabolism in gastric cancer in the not-too-distant future.

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