Metabolic reprogramming results in abnormal glycolysis in gastric cancer: a review

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Abstract: The Warburg effect in tumor cells involves the uptake of high levels of glucose, enhanced glycolysis, and the metabolism of pyruvate to lactic acid rather than oxidative phosphorylation to generate energy under aerobic conditions. This effect is closely related to the occurrence, invasion, metastasis, drug resistance, and poor prognosis of gastric cancer (GC). Current research has further demonstrated that the Warburg effect in GC cells is not only mediated by the glycolysis pathway, but also includes roles for mitochondria, noncoding RNAs, and other proteins that do not directly regulate metabolism. As a result, changes in the glycolysis pathway not only lead to abnormal glucose metabolism, but they also affect mitochondrial functions, cellular processes such as apoptosis and cell cycle regulation, and the metabolism of lipids and amino acids. In this review, we discuss metabolic reprogramming in GC based on glycolysis, a possible link between glucose metabolism, lipid metabolism, and amino acid metabolism, and we clarify the role of mitochondria. We also examine recent studies of metabolic inhibitors in GC.

Keywords: gastric cancer, glycolysis, mitochondria, metabolic reprogramming, Helicobacter pylori

Introduction

Gastric cancer (GC) is currently one of the most common malignant tumors diagnosed, and it is the second leading cause of mortality due to cancer.¹ GC originates in gastric epithelial cells and similar to other types of tumors, it exhibits a Warburg effect. This effect involves a high uptake of glucose, enhanced glycolysis, and the metabolization of a large amount of pyruvate to lactic acid rather than oxidative phosphorylation to provide energy under aerobic conditions.² The metabolic changes dominated by the Warburg effect have recently been referred to as metabolic reprogramming, and studies of these changes have provided a deeper understanding of tumor cell metabolism. For example, it has been demonstrated that GC cells and normal cells exhibit metabolic differences not only in glucose metabolism, but also in the metabolism of lipids and amino acids. Accordingly, a large number of specific biomarkers of GC have been identified. Metabolic reprogramming of GC has also been recognized as a novel approach for the study of the biological characteristics of GC.

In this review, we focus on a discussion of recent insights into the glycolysis pathway in GC and we summarize the complex relationship that exists between glucose metabolism, lipid metabolism, and amino acid metabolism. The role and impact of mitochondrial function in each of these aspects are also considered.
**Helicobacter pylori** promotes the genesis of GC by inducing metabolic reprogramming

Infection by *Helicobacter pylori* (Hp) is the most important primary cause of GC. However, progression from a Hp infection to atrophic gastritis and eventually GC is a long-term process. In vitro, Hp-infected gastric epithelial cells have exhibited increased glycolysis and increased expression of Lon protease 1 (Lonp1), a protein that activates the mitochondrial unfolded protein response and maintains mitochondrial function. Correspondingly, knockdown of Lonp1 has been shown to reverse alterations in metabolism that are caused by Hp, thereby suggesting that aerobic glycolysis and mitochondrial dysfunction correlate with the genesis of GC. Hp-induced GC is also characterized by higher expression levels of the M2 isoform of pyruvate kinase, PKM2, among other factors that are induced in GC and that affect mitochondrial function. Cytoxin-associated gene A (CagA) has been shown to upregulate expression of PKM2 and pyruvate dehydrogenase kinase (PDK1). Moreover, when CagA localizes to mitochondria, it inhibits the activity of sirtuin 3 (SIRT3) and promotes stability of hypoxia-inducible factor 1α (HIF-1α). Vacuolating cytotoxin A (VacA) is another Hp protein, and it has been shown to trigger mitochondrial dysfunction, promote mitochondrial division, and reduce mitochondrial DNA (mtDNA) copy number. Taken together, these findings support a model in which Hp induces GC by promoting glycolysis and mitochondrial dysfunction (Table 1).

### Molecular factors that affect metabolic reprogramming in GC cells

Metabolic reprogramming that occurs in GC mainly involves changes in the following molecular factors: 1) key enzymes in glycolysis, 2) mitochondrial proteins, 3) noncoding RNAs, and 4) proteins that regulate these factors. The changes manifested by these molecules include significant differences in their levels between GC tissues and normal tissues. Moreover, interventions targeting these molecules have been found to not only affect the metabolic profile of GC cells, but also to affect the genesis, proliferation, invasion, and metastasis of GC cells as we describe below.

#### Changes in key glycolysis enzymes during metabolic reprogramming in GC

The glycolysis profile of GC is unique and is based on the ability of GC cells to maintain their growth under hypoxic conditions, to provide raw materials for cell biosynthesis and cell division, and to maintain intracellular redox homeostasis. These functions also correlate with the genesis, proliferation, invasion, and metastasis of GC cells. The following six proteins have been identified as key glycolytic enzymes that are affected by metabolic reprogramming in GC (Figure 1).

#### Hexokinase II

The hexokinase (HK) family of proteins catalyzes the conversion of glucose to glucose 6-phosphate (G6P) as the first rate-limiting step in glycolysis. G6P also participates in the pentose phosphate pathway and the process of gluconeogenesis. Among the HK family of proteins, HKII has been found to be consistently overexpressed in most tumors, including GC. HKII is also associated with poor prognosis of GC in most cases. HKII binds to voltage-dependent anion channels (VDACs) on the outer membrane of mitochondria to obtain ATP that is required for glycolysis. However, HKII can also bind to the outer membrane of mitochondria, specifically via the antiapoptotic protein, Bcl-2, and the proapoptotic protein, Bax, to inhibit apoptosis. Thus, HKII is an excellent target for blocking glucose flux.

#### Pyruvate kinase M2

Pyruvate kinase (PK) is a key enzyme in the final step of glycolysis, which catalyzes the conversion of phosphoenolpyruvate...
to pyruvate. There are four members of the PK protein family, PKM1, PKM2, PKL, and PKR. PKM1 and PKM2 are encoded by PKM, while PKL and PKR are encoded by the PKLR gene. In addition, PKM1 exhibits PK activity, yet PKM2 does not. Tumor cells generally express high levels of PKM2 and low levels of PKM1, thereby promoting glycolysis and inhibiting mitochondrial oxidative phosphorylation. When PKM2 was knocked out in GC cells, the PI3K/AKT/mTOR pathway and autophagy were inhibited, thereby leading to a decrease in the proliferation and invasive phenotype of GC cells. PKM2 can also translocate to the nucleus and promote transcription of HIF-1α and Bcl-xL to further enhance glycolysis. Moreover, interactions between PKM2, β-catenin, and octamer-binding transcription factor 4 (OCT4) have been shown to maintain the stemness quality of cells. In mitochondria, PKM2 interacts with and activates Bcl-2 to inhibit apoptosis. Correspondingly, overexpression of PKM2 promotes mitochondrial fusion, fewer copies of mtDNA, and the expression and degradation of p53. Overexpression of PKM2 also reduces levels of electron transport chain complex proteins I, III, and V. Taken together, these studies indicate that PKM2 promotes glycolysis and contributes to the dysfunction of mitochondria.

Pyruvate dehydrogenase kinase

The PDK family of proteins includes four isoforms. Many studies have recently focused on PDK1, which is generally expressed at high levels in tumors and is associated with tumor proliferation, metastasis, and poor prognosis. PDK1 inhibits the activity of pyruvate dehydrogenase (PDH) to promote the metabolization of pyruvate to lactic acid, and it helps regulate the AKT/NF-κB pathway. The ability of PDK to inhibit PDH activity also leads to a decrease in the level of acetyl-CoA to influence the de novo synthesis of lipids.

Enolase

Enolase (ENO1) catalyzes the conversion of phosphoglycerol to phosphoenolpyruvate in glycolysis and is highly expressed in GC. Knockdown of ENO1 has been shown to inhibit glycolysis and increase the sensitivity of GC cells to cisplatin. Conversely, overexpression of ENO1 enhances the proliferation and metastasis of GC cells. In a proteomic analysis, ENO1 was found to be closely related to heat shock protein beta-1 (also known as Hsp27), while it has also been found to affect the regulation of anti-stress pathways.

Glucose transporter

As implied by their name, glucose transporters (GLUTs) 1–4 are responsible for the transport of glucose into cells, and in GC, where GLUT1 and GLUT4 are highly expressed. When GLUT1 was knocked out in GC cells in vitro, metabolic reprogramming was significantly reversed and apoptosis was triggered. Levels of HK2 and PKM2 also declined in the absence of GLUT1. Conversely, upregulation of GLUT4 by p38 mitogen-activated protein kinase affects myocyte enhancer factor 2α and promotes glycolysis.

Lactate dehydrogenase

Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactic acid and is a key enzyme in the metabolic reprogramming of tumors. LDH is highly expressed in GC and promotes glycolysis. In GC, the transcription factor, fork head/winged-helix 1, upregulates the M isoform of LDH, LDHA. Meanwhile, downregulation of LDHA by OCT4 has been associated with a good prognosis in GC.

Association between mitochondria and metabolic reprogramming in GC

Mitochondria are the energy factories for cells and their functions are often compromised in tumors. While dysfunctional mitochondria have been recently shown to promote tumor survival, the underlining mechanism(s) remain to be elucidated. Here, we describe three aspects of mitochondrial function in GC.

MtDNA

Low levels of mtDNA have been shown to have an important effect on the biogenesis and homeostasis of mitochondria. In 62.5% of GC patients, mutations in mitochondrial genes have been identified. A decrease in mtDNA copy number has also been observed in 54.8% of GC patients, especially patients affected by advanced GC. Furthermore, it has recently been reported that curcumin suppresses the growth of GC by increasing the production of ROS to mediate depletion of DNA polymerase gamma. These changes affect mitochondrial oxidative phosphorylation and inhibit cell biosynthesis.

Mitochondrial topoisomerase I

Replication of mtDNA requires topoisomerases, except for mitochondrial topoisomerase I (TOP1MT). The latter exerts a negative effect on the regulation on mtDNA replication, yet plays an important role in the formation and maintenance of D-LOOP regions of mtDNA and in maintaining mitochondrial homeostasis. Thus, low levels of TOP1MT are generally expressed in GC. In the absence of TOP1MT, oxidative stress and mitochondrial autophagy are induced.
glycolysis is promoted, the epithelial–mesenchymal transition (EMT) is accelerated, and the proliferation, invasion, and metastasis of GC cells are enhanced. Expression of LDHA and glycolysis are also increased in the absence of TOP1MT, thereby indicating that TOP1MT affects cell proliferation by modulating glycolysis. In clinical studies of GC, TOP1MT has been associated with poor prognosis.

**SIRT3**

SIRT3 localizes to mitochondria and is mainly involved in regulating oxidative stress. However, SIRT3 has also been shown to upregulate manganese-dependent superoxide dismutase, inhibit mitochondrial ROS levels, regulate the unfolded protein response of mitochondria, and maintain mitochondrial homeostasis. Thus, SIRT3 is considered a tumor suppressor gene. However, there are conflicting data regarding the role of SIRT3 in GC. For example, expression of SIRT3 in GC tissues has been found to be lower in some studies, and higher in others, than in normal tissues. Similarly, overexpression of SIRT3 has been associated with a significant reduction in cell proliferation, and conversely, has also been associated with enhanced cell proliferation. When SIRT3 was overexpressed in GC cells, promotion of ATP production and glycolysis were observed. Moreover, SIRT3 has been shown to acetylate LDHA to enhance its LDH activity. In the clinic, patients with high levels of SIRT3 expression have been associated with good prognosis. Thus, the role of SIRT3 in GC remains an area of research, and inconsistencies among reported results remain to be resolved.

Despite advances in characterizing mitochondrial factors and their roles in metabolic reprogramming in GC, there have been very few studies that have examined the relationship between mitochondria and metabolic reprogramming. However, as described above, the localization of glycolysis-related proteins to mitochondria can affect the functions of mitochondria, while mitochondrial proteins can also affect glycolysis. Thus, it appears that mitochondria are tightly linked with metabolic reprogramming that occurs, and this complex relationship remains to be thoroughly characterized.

**The effect of other molecules on metabolic reprogramming in GC**

There are other types of molecules which can regulate glycolysis and mitochondrial function in GC, and we introduce some of these molecules below. These representative molecules demonstrate how metabolic reprogramming can correlate with the EMT, cell cycle, and other cellular processes.

**Snail**

Snail is a key molecule in the EMT process and also regulates glycolysis. When Snail is overexpressed in GC cells, glucose intake is increased while activity of fructose bisphosphatase 1 is inhibited. In GC, overexpression of Snail has been shown to correlate with metastasis and poor prognosis.

**Hypoxia-inducible factor 1α**

HIF-1α is a key factor for cell survival under hypoxic conditions. In GC, HIF-1α is highly expressed and is closely related to poor prognosis and drug resistance. The level of HIF-1α expression in GC metastases has also been found to be higher than that in primary tumors, and it appears to promote GC metastasis by inhibiting integrin 5α.

**Thymidine phosphorylase**

Thymidine phosphorylase (TP) catalyzes the conversion of thymidine to thymine and 2-deoxy-D-ribose 1-phosphate. In GC, TP activates the NF-κB pathway to promote angiogenesis, lymphangiogenesis, and metastasis. Under conditions of nutritional deprivation, thymidine provides a carbon source for glycolysis, and a high level of thymidine catabolism has been observed in GC.

**Monocarboxylic acid transporter**

The monocarboxylic acid transporter (MCT) family of proteins has 14 members. In GC, MCT1, MCT2, and especially MCT4, are highly expressed. These proton pumps transport monocarboxylic acids, pyruvic acid, lactic acid, ketone bodies, and other substances to maintain high glucose flux. They also play an important role in cell survival under highly acidic conditions in tumor cells. Moreover, expression of MCT4 has also been associated with advanced tumor size-lymph nodes-metastases staging of GC.

**p53**

p53 is a tumor suppressor protein which plays an important role in cell cycle arrest, apoptosis, DNA repair, and glycolysis. Currently, it is widely accepted that wild-type (WT) p53 inhibits glycolysis and promotes oxidative phosphorylation. For example, WT p53 downregulates GLUT1/4 and GLUT3 by inhibiting NF-κB signaling, thereby reducing the intracellular flux of glucose. WT p53 can also inhibit expression of HKII at the transcriptional level and upregulate the protein, parkin, to induce ubiquitination of PKM2 and inhibit glycolysis. In addition, WT p53 is able to inhibit glycolysis by upregulating TP53-induced glycolysis and the apoptosis regulator, TIGAR.
have been detected in >50% of cancer patients.\textsuperscript{57} Mutant p53 proteins have also been shown to mediate functions that oppose those of WT p53. For example, mutant p53 proteins have been shown to promote glycolysis in tumors via upregulation of GLUT1, GLUT4, and HKII.\textsuperscript{58} In GC, mutant p53 inhibits TIGAR, thereby enhancing glycolysis, and it correlates with poor prognosis.\textsuperscript{59,60}

Effect of noncoding RNAs on metabolic reprogramming in GC

Noncoding RNAs, including microRNAs and long noncoding RNAs (lncRNAs), mediate complex regulatory effects on the structure, function, and processes of cells.\textsuperscript{61} It has been reported that microRNAs and lncRNAs regulate key molecules involved in the metabolism of glucose to influence the proliferation, invasion, and metastasis of GC.\textsuperscript{62,63}

Effect of microRNAs on metabolic reprogramming in GC

Various microRNAs have been shown to regulate glycolysis in GC. For example, Mir-22 upregulates ENO1.\textsuperscript{64} Mir-186 inhibits the activity of HIF-1\(\alpha\), thereby leading to an increase in glucose uptake, lactate production, ATP/ADP, and a decrease in NAD\(^+\)/NADH.\textsuperscript{65} Mir-let-7a inhibits GC progression by inhibiting PKM2,\textsuperscript{66} while Mir-133b inhibits poly pyrimidine tract-binding protein 1 to reduce levels of PKM2.\textsuperscript{67} Mir-181b reduces glucose intake and increases ATP production via inhibition of HKII expression.\textsuperscript{68} Furthermore, Mir-448 maintains glycolysis levels by inhibiting KDM2B.\textsuperscript{69} Mir-148 enhances glycolysis by upregulating GLUT1.\textsuperscript{70} Mir-375 inhibits expression of PDK1,\textsuperscript{71} and Mir-128b binds the 3' UTR of PDK1 to inhibit expression of PDK1.\textsuperscript{72}

Effects of lncRNAs on metabolic reprogramming in GC

Various lncRNAs have also been shown to regulate glycolysis in GC. For example, the lncRNA, MACC1-AS1, has been shown to enhance MET-related transcription factor 1 (MACC1), activate the AMPK-LIN28 pathway, enhance glycolysis and the antioxidant capacity of GC cells, and play a cancer-promoting role in GC.\textsuperscript{73} Correspondingly, MACC1 is associated with poor prognosis in GC. Recent studies have further shown that MACC1 contributes to resistance to trastuzumab in GC via activation of the PI3K/AKT signaling pathway.\textsuperscript{74} Under conditions of nutritional deprivation, AMPK upregulates levels of MCAAI, while levels of HKII, PDK1, and LDH are also upregulated under these conditions.\textsuperscript{75} Lnc00152 promotes GC by inhibiting miR-139-5p, although miR-139-5p is able to inhibit glycolysis by upregulating AMP-activated protein kinase 1\(\alpha\) (PRKAA1).\textsuperscript{76} Finally, IncTINCR is a molecular sponge of miR-375, and it promotes expression of PDK1 and proliferation and metastasis in GC.\textsuperscript{77}

The effects of lipid metabolism and amino acid metabolism on metabolic reprogramming in GC

Intracellular pathways for the metabolism of lipids, amino acids, and glucose are needed for life, and they are closely linked with each other. Correspondingly, in cancer cells, abnormal glucose metabolism is often accompanied by changes in the metabolism of lipids and amino acids.

Effect of lipid metabolism on metabolic reprogramming in GC

In GC, levels of lipids and triglycerides generally increase.\textsuperscript{78} In a metabolomic analysis of GC cells, low levels of 3-hydroxybutanoic acid (the end product of fatty acid \(\beta\)-oxidation) and inhibition of cholesterol synthesis were detected.\textsuperscript{28} A metabolic analysis of a rat GC model also showed that oxidative stress-related pathways, fatty acid degradation, and amino acid metabolism were all blocked.\textsuperscript{79}

Endoscopic explorations have revealed a novel ultrastructure for GC, which includes a white opaque substance (WOS). Histology studies further revealed that the interior of this WOS consists of a large number of lipid drops. This novel structure is considered to be a hallmark of GC, and its formation is consistent with observations that lipid degradation is inhibited and lipid synthesis is enhanced in GC. The latter processes also contribute to an accumulation of lipids intracellularly.\textsuperscript{79,80} Meanwhile, if lipid metabolism is compromised, low levels of mitochondrial oxidative phosphorylation are observed, and this may be related to poor prognosis in GC.\textsuperscript{81} Correspondingly, when a ketogenic diet consisting of average protein content, low levels of carbohydrates, and enriched omega-3 fatty acid and medium-chain triglyceride content was fed to a nude mouse GC metastasis model, reduced glucose uptake and significant inhibition of GC growth were observed.\textsuperscript{82}

The effect of amino acid metabolism on metabolic reprogramming in GC

Metabolomic analyses have shown that the concentration of leucine, a ketogenic amino acid, is significantly reduced in GC, while levels of glycine, phenylalanine, and arginine are significantly increased.\textsuperscript{28} In addition, the amino acid
transporter gene, *LAT1*, has been shown to be upregulated in GC cell membranes. In GC cells subjected to glucose deprivation, nonessential amino acids can prevent activation of the mitochondrial apoptosis pathway by maintaining mitochondrial homeostasis and a stable mtDNA copy number. The ability of PKM2 to act as a sensor of amino acids has also recently been demonstrated. In particular, phenylalanine, alanine, tryptophan, methionine, valine, and proline are able to inhibit it, and histidine and serine are able to activate PKM2. These findings suggest that amino acids can influence glucose metabolism in a more complex manner than previously anticipated, and a further study of this relationship is needed.

**Novel metabolic inhibitors for treatment of GC**

There are many new drugs that have been designed to target the glycolysis pathway, and many of these induce cell apoptosis. Below, we describe various metabolic inhibitors that have been developed to target four of the six glycolysis targets listed in Section “Molecular factors that affect metabolic reprogramming in GC cells”, as well as HIF-1α.

**Targeting of key glycolysis enzymes**

**Targeting HKII**

HKII binds to VDACs or Bcl-2 in combination with Bax on the outer membrane of mitochondria to obtain ATP for glycolysis, or to inhibit apoptosis, respectively. Both 3-BrPA, an inhibitor of HKII, and SCT, an inhibitor of phosphate fructose kinase, downregulate Bcl-2 and upregulate Bax, to inhibit glycolysis and enhance mitochondria-associated apoptosis. Meanwhile, 2-deoxy-D-glucose has been shown to competitively combine with HKII to block glucose flux. Glycolysis activity is also reduced when baicalein inhibits HKII, PDK1, and LDHA, and baicalein has been shown to reduce the resistance of stomach adenocarcinoma cells to fluorouracil. Furthermore, licorice chalcone A is a novel HKII inhibitor, as well as an inhibitor of the AKT pathway, which has been shown to reduce glucose consumption and lactate production in GC cells, with the latter condition inducing apoptosis.

**Targeting PKM2**

As described above, PKM2 has various roles in a cell. Thus, inhibitors that target this protein exhibit various effects. For example, inhibition of PKM2 in GC cells by LY294002 induces apoptosis. Meanwhile, pantoprazole (PPZ), a third-generation proton pump inhibitor and a newly identified PKM2 inhibitor, inhibits the Akt/GSK-β/β-catenin pathway and reverses sensitivity to chemotherapy in GC cells. PPZ has also been shown to reverse chemotherapy resistance in SGC7901 cells by downregulating V-ATPases/mTOR/HIF-1α/P-gp and MRP1 signaling pathways. Furthermore, inhibition of PKM2 by resveratrol induces endoplasmic reticulum stress in tumor cells, promotes mitochondrial division, and leads to apoptosis in tumor cells. Accordingly, overexpression of PKM2 has been shown to relieve the effect of resveratrol.

**Targeting of PDK1 and LDH**

Dichloroacetate has been shown to inhibit PDK1 and activate mitochondrial oxidative phosphorylation in GC cells, thereby resulting in an accumulation of mitochondrial ROS and apoptosis. Meanwhile, oxamate is an LDH inhibitor, which inhibits mTOR activity, increases levels of ROS, and induces apoptosis in GC cells.

**Targeting of HIF-1α**

YC-1 is an inhibitor of HIF-1α, which reduces glycolysis and increases oxidative phosphorylation and intracellular ROS levels in GC cells. Under hypoxic conditions in vitro, treatment of GC cells with YC-1 has led to apoptosis. Similarly, rosmarinic acid is another inhibitor of HIF-1α, which reduces glycolysis and induces apoptosis in GC cells.

While none of these drugs are currently available for clinical use, they have the potential to facilitate in vitro and/or in vivo studies of glycolysis to elucidate mechanistic details.

**Conclusion**

It is clear that a complex relationship exists among the pathways responsible for the metabolism of lipids, amino acids, and glucose, although the components, interactions, and regulatory mechanisms associated with these fundamental pathways remain to be fully characterized. In addition, it has been demonstrated that mitochondria play an important role in metabolic reprogramming in GC, not only by regulating oxidative phosphorylation, but also by regulating the metabolism of lipids and amino acids (Figure 2). An important observation regarding the studies conducted to date involves differences in the results of in vitro vs in vivo studies. For example, in vitro studies involving low-glucose media have exhibited higher degrees of malignancy and drug resistance than in vivo studies. Therefore, it is important for future studies to identify and optimize in vitro experimental conditions so that they are consistent with in vivo conditions. As a result, effects that are cell-specific and/or pathology-specific
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