Helicobacter pylori and hyperglycemia fuel gastric cancer glycolysis: Mechanisms and targeted intervention (Review)

YOUJIA LIU[1-3*], FANG WANG[1-3*], YA DENG[2], YANXIA HU[2], FEIHONG SHU[2], JIE YU[2], GUOYOU GOU[2], MIN WEN[2], CHEN LUO[2], XIANMIN LU[2], QIAN DU[1], JINGYU XU[2] and RUI XIE[1,3]

[1]Department of Endoscopy and Digestive System, Guizhou Provincial People's Hospital, Guiyang, Guizhou 550002, P.R. China; [2]Collaborative Innovation Center for Tissue Repair and Regenerative Medicine, Zunyi Medical University, Zunyi, Guizhou 563006, P.R. China; [3]Guizhou Provincial Key Laboratory for Digestive System Diseases, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550002, P.R. China

Received May 31, 2025; Accepted November 28, 2025

DOI: 10.3892/ijmm.2026.5763

Abstract. *Helicobacter pylori* (*H. pylori*) is a Gram-negative bacterial pathogen, and infection with this pathogen is a primary risk factor for gastric cancer (GC), often inducing chronic gastritis, which further increases the risk of cancer. Glycolysis carries out a key role in GC metabolism, serving as the primary energy pathway for cancer cells, particularly under hypoxic conditions. Enhanced glycolysis allows GC cells to sustain high proliferation rates and produce lactic acid, creating an acidic tumor microenvironment that promotes tumor progression. Understanding the mechanisms of *H. pylori*-driven glycolysis may provide new insights into GC pathogenesis and reveal novel therapeutic targets. The present review addresses advances in glycolysis research in GC, summarizing its characteristics, identifying key mediators involved in metabolic reprogramming and exploring potential molecular mechanisms to recommend new targets for therapy.

Correspondence to: Professor Jingyu Xu, Collaborative Innovation Center for Tissue Repair and Regenerative Medicine, Zunyi Medical University, 1 Campus Road, Zunyi, Guizhou 563006, P.R. China
E-mail: xujingyu_gzzy@126.com

Professor Rui Xie, Department of Endoscopy and Digestive System, Guizhou Provincial People's Hospital, 395 Jinzhu East Road, Guiyang, Guizhou 550002, P.R. China
E-mail: xr19841029@aliyun.com

*Contributed equally

Abbreviations: H. pylori, *Helicobacter pylori*; GC, gastric cancer; CagA, Cytotoxin-associated gene A; Cag PAI, Cag pathogenicity island; VacA, vacuolating cytotoxin A; IGF, insulin-like growth factor; IR-A, insulin receptor isoform A; ROS, reactive oxygen species; TME, tumor microenvironment; ECM, extracellular matrix; TAMs, tumor-associated macrophages; PDK1, 3-phosphoinositide-dependent protein kinase 1; CAF, cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; GLUT, glucose transporter; HK2, hexokinase 2; OXPHOS, oxidative phosphorylation; ETC, electron transport chain; TCA cycle, tricarboxylic acid cycle; LDH, lactate dehydrogenase; PKM2, pyruvate kinase M2; 5-FU, 5-fluorouracil

Key words: gastric cancer, metabolic reprogramming, *Helicobacter pylori* infection, Warburg effect, glycolysis, metabolism-targeted therapy, tumor microenvironment

Contents

1. Introduction

GC is a global health issue. According to 2022 GLOBOCAN data, GC ranks as the 5th most common malignancy worldwide and is a leading cause of cancer-related mortality (1). In China, the incidence of GC is the 5th highest compared with all types of cancer (2,3). *Helicobacter pylori* (*H. pylori*) infection is recognized as one of the most pronounced pathogenic factors for GC. In 1994, the International Agency for Research on Cancer of the World Health Organization classified *H. pylori* as a Group 1 (definite) carcinogen associated with GC (4). Among individuals infected with *H. pylori*, ~60% of the general population is infected or has been previously infected with *H. pylori*, with the infection rate reaching as ≤84% among patients with GC (5). Despite improvements in living standards and sanitation leading to a decline in the global GC incidence and mortality, it remains one of the major causes of mortality (6).

Glycolysis is a fundamental metabolic pathway widely studied in cancer, especially within tumor cell metabolism, where it serves as a key component. The present review

emphasizes that glycolysis should not be rigidly classified as 'aerobic' or 'anaerobic' since lactate may be the end product of glycolysis regardless of oxygen availability (7). Unless otherwise specified, the term 'glycolysis' in the present review predominantly refers to aerobic glycolysis, the Warburg effect, in which cancer cells preferentially metabolize glucose to lactate even in the presence of sufficient oxygen. This process is distinct from anaerobic glycolysis, which occurs under hypoxic conditions as a compensatory energy pathway when oxidative phosphorylation is limited. While both processes share the common endpoint of converting glucose into lactate, aerobic glycolysis is a hallmark of several types of cancer, enabling rapid ATP generation and supporting the biosynthetic demands necessary for tumor cell proliferation. GC cells typically exhibit enhanced glycolytic activity. During cancer cell proliferation, the metabolic phenotype shifts to increased glycolysis and lactate production to meet the elevated energy and biosynthesis requirements (8,9). Currently, research primarily focuses on the role of glycolysis in gastrointestinal stromal tumors and colorectal cancer (10,11). However, the specific mechanisms of glycolysis in GC and their impact on GC progression remain insufficiently understood.

The present review aims to investigate the specific mechanisms which drive glycolysis in the development and progression of GC. By analyzing the relationship between the expression of glycolysis-related enzymes and the prognosis of GC, the present review aims to elucidate the effects of glycolytic pathways on the growth, invasion and drug resistance of GC cells. The present study also focuses on the impact of *H. pylori* infection on the glycolytic pathways in GC. Given the key role of metabolic reprogramming in GC, therapeutic strategies targeting these pathways, collectively termed metabolism-targeted therapy, hold potential. Such approaches may include inhibiting key glycolytic enzymes, disrupting *H. pylori*-induced metabolic adaptations or modulating the tumor microenvironment (TME), with the potential to improve outcomes and overcome drug resistance.

2. Combined effect of *H. pylori* and hyperglycemia in the pathogenesis of GC

H. pylori and the pathogenic mechanisms of GC. Current research indicates that *H. pylori* exerts carcinogenic effects on the gastric mucosa through a complex interaction of bacterial, host and environmental factors. *H. pylori*-induced carcinogenesis can be broadly divided into two mechanisms: i) Those based on the induction of chronic inflammation and ii) those associated with *H. pylori*-specific virulence factors.

H. pylori-induced carcinogenesis via chronic inflammation. Infection by *H. pylori* and the ensuing chronic inflammation of the gastric mucosa represent key steps in the initiation and progression of GC. *H. pylori* infection can upregulate various pro-inflammatory cytokines, which trigger an inflammatory response. Among these cytokines, the activation of NF-κB and the upregulation of IL-8 are considered key mechanisms underlying *H. pylori*-induced chronic inflammation and GC development (12). Activation of Jak1/Stat3 mediates NF-κB activation and increases IL-8 upregulation in AGS cells infected by *H. pylori* (13).

Carcinogenesis via specific virulence factors. Among all virulence factors, CagA pathogenicity island and VacA are considered the most important. Both phosphorylated and non-phosphorylated CagA can extensively interact with numerous host proteins to activate downstream signaling pathways, leading to disorganization of gastric epithelial cell polarity and initiation of pro-inflammatory responses (12,14).

Additionally, VacA exhibits various biological activities such as binding to and being internalized by host cells to induce notable cellular vacuolization. It also disrupts epithelial tight junctions, and inhibits T lymphocyte activation and proliferation within the lamina propria, and releases pro-inflammatory factors such as IL-6, IL-8 and TNF-α further intensifying the local inflammatory environment (15,16) (Fig. 1). Through the pathogenic effects of CagA or the chronic inflammation it induces, *H. pylori* can promote GC progression by exacerbating aberrant DNA methylation patterns, especially hypermethylation of tumor suppressor genes (17).

Glycolytic activity has been shown to upregulate immune checkpoint expression, suggesting that glycolysis may enhance responses to immunotherapy and predict its efficacy (18). Hypoxia inducible factor (HIF)-1α, a transcriptional regulator of immune and oncogenic responses, associates with the severity of gastric lesions. *H. pylori* infection markedly upregulates HIF-1α expression and increases reactive oxygen species (ROS) in human gastric epithelial cells, promoting cell cycle arrest in G_0/G_1 and slowing the progression of precancerous gastric lesions (19-21).

Hyperglycemia contributes to H. pylori colonization and susceptibility. Hyperglycemia is associated with the release of pro-inflammatory factors, oxidative stress, impaired immune function and increased insulin secretion (20,21). *H. pylori* infection induces metabolic disturbances mediated by inflammatory cytokines produced in the gastric mucosa. Evidence suggests that hyperglycemia and GC share common risk factors, which may synergize with *H. pylori* infection to promote GC (22).

Under high-glucose conditions, *H. pylori* can maintain growth and viability for up to 48 h. The growth and adhesion abilities of *H. pylori* are enhanced, further promoting the expression of virulence factors associated with its type IV secretion system (23). Glycated hemoglobin (HbA1c) is the most valuable indicator of long-term blood glucose control. An epidemiological study by Ikeda *et al* assessed the interaction between HbA1c levels and the incidence of GC, indicating that hyperglycemia increases the risk of GC associated with *H. pylori* infection (24). A study reported that persistently impaired fasting glucose is associated with an increased risk of several types of cancer, with gastrointestinal types of cancer showing a dose-dependent association (25). Among patients without a diabetes diagnosis, research has found a positive association between blood glucose levels and cancer mortality rates, with hyperglycemia promoting GC cell proliferation and reducing sensitivity to chemotherapeutic agents (26).

The enhanced colonization of *H. pylori* in hyperglycemic conditions is associated with several factors: Diabetes-induced impairments in cellular and humoral immunity may increase susceptibility to *H. pylori* infection; prolonged *H. pylori* infection combined with high glucose levels disrupts the

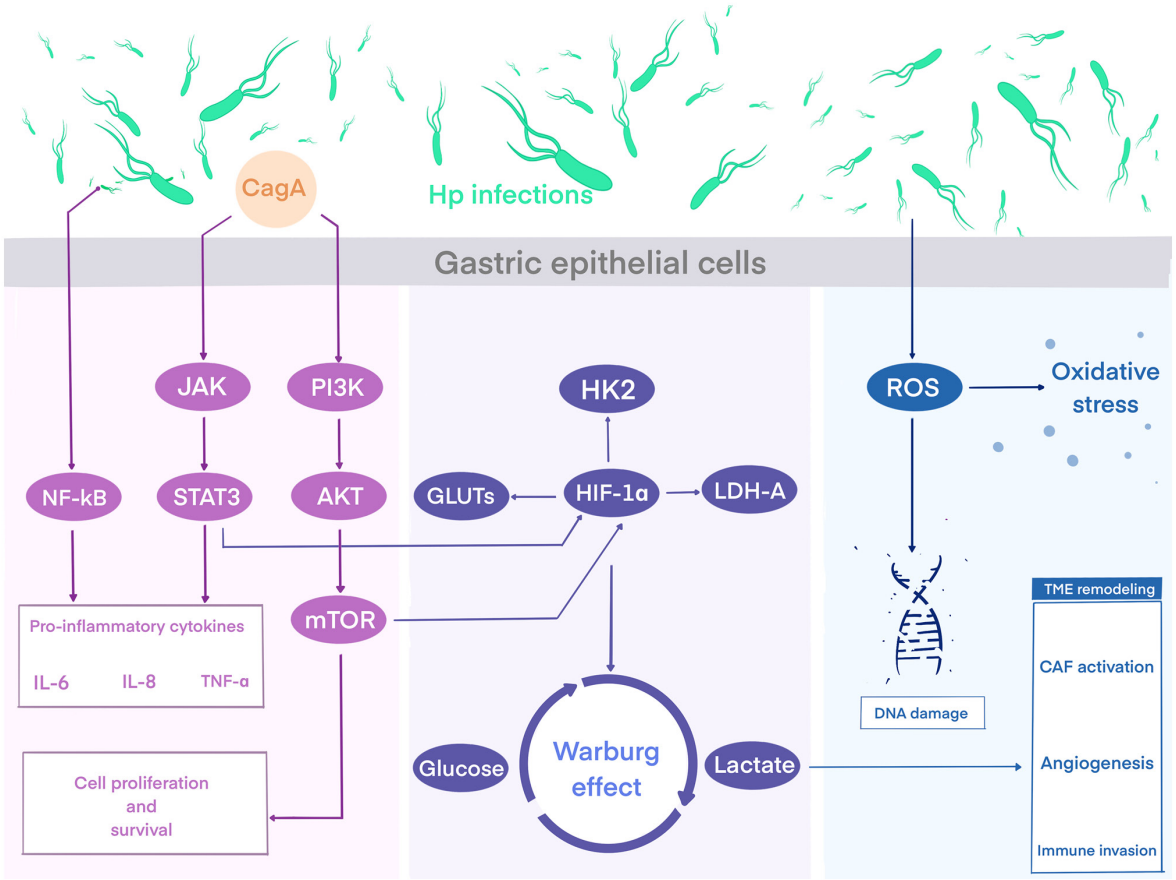

Figure 1. *H. pylori*-induced inflammatory and oxidative pathways converge on glycolytic reprogramming to drive GC progression. Pathogenic mechanisms of *H. pylori* infection in GC. The virulence factor CagA activates JAK/STAT3, NF-κB and PI3K/AKT/mTOR pathways, inducing pro-inflammatory cytokines (IL-6, IL-8 and TNF-α) and promoting cell proliferation. These signals upregulate glycolytic regulators (HIF-1α, GLUTs, HK2 and LDH-A), driving the Warburg effect with increased glucose uptake and lactate production. Concurrently, *H. pylori* stimulates ROS generation, leading to oxidative stress, DNA damage and tumor microenvironment remodeling, including CAF activation, angiogenesis and immune cell infiltration. Figure created using Procreate: Savage Interactive Pty Ltd (Version 5.4.7) and Adobe Illustrator (Adobe Inc 2025; Version 29.x). *H. pylori*, *Helicobacter pylori*; GC, gastric cancer; CagA, cytotoxin-associated gene A; HK2, Hexokinase 2; ROS, reactive oxygen species; GLUTs, glucose transporters; HIF-1α, hypoxia-inducible factor 1-α; LDH-A, lactate dehydrogenase A; TNF-α, tumor necrosis factor α; CAF, cancer-associated fibroblasts.

gastrointestinal microbiota, reduces gastric acid secretion and slows gastrointestinal motility, creating an environment conducive to *H. pylori* colonization (27); changes in glucose metabolism may alter the gastric mucosa, facilitating *H. pylori* colonization (23) and diabetic patients have higher health-care utilization rates, implying more frequent exposure to pathogens (28).

H. pylori increases insulin resistance. *H. pylori* infection may lead to chronic inflammatory responses in the gastrointestinal tract, participating in immune responses by producing inflammatory factors. Studies indicate that inflammation may trigger and ultimately increase insulin resistance. Compared with patients that are *H. pylori*-negative, those infected with *H. pylori* show elevated levels of IL-6 and TNF-α (29-31). The pro-inflammatory cytokine, IL-6, has been recognized as one of the earliest predictors or pathogenic mediators of insulin resistance, while TNF-α has been shown to exacerbate insulin resistance (32). *H. pylori* employs its virulence factors, CagA and VacA, to upregulate pro-inflammatory cytokines and activate the NF-κB signaling cascade (33). Under normal conditions, NF-κB remains inactive; however, factors such as insulin resistance, inflammatory mediators and disruptions in glucose and lipid metabolism can trigger the NF-κB signaling cascade within cells (34). NF-κB directly induces the production of pro-inflammatory cytokines, including TNF-α and IL-6, thereby initiating inflammatory responses (35). Through its signaling pathways, NF-κB impacts various interconnected organs, influencing glucose metabolism disorders (36).

H. pylori increases gastric hormone secretion. The presence of *H. pylori* influences metabolism by regulating hormones and markedly altering the gut microbiota. Ghrelin and leptin are key hormones in human energy homeostasis: Leptin suppresses food intake in response to satiety, while ghrelin stimulates appetite (37). *H. pylori* not only indirectly regulates energy homeostasis by altering gut microbiota composition but also directly modulates leptin and ghrelin secretion (38,39). *H. pylori*-induced gastric mucosal damage leads to increased leptin and gastrin levels, while plasma ghrelin levels decrease (40).

Research by Açbay *et al* showed that *H. pylori* acts as a physiological amplifier of insulin release, potentially enhancing insulin secretion in response to glucose and dietary stimulation by increasing gastrin secretion (41), while also inhibiting glucose absorption in the small intestine (42).

However, Verhulst and Depoortere (43) found a negative feedback mechanism between ghrelin and insulin, which raises circulating glucose levels (44).

Similarly, in the gastric mucosa of *H. pylori*-infected Mongolian gerbils, ghrelin levels decreased due to infection (45). These findings suggest that *H. pylori* infection negatively impacts ghrelin dynamics in the stomach and plasma, increasing insulin secretion by lowering serum ghrelin concentrations, which subsequently inhibits insulin release.

Additionally, a clinical study indicated higher insulin resistance in *H. pylori*-infected individuals (46). This suggests an association between *H. pylori* infection,-decreased ghrelin, and increased leptin levels, associated with disrupted energy homeostasis, elevated fasting insulin levels and reduced insulin sensitivity.

H. pylori activates signaling pathways. In exploring the mechanisms underlying the progression of GC, the present review identified multiple key molecular targets and signaling pathways. The innate immune response triggered by *H. pylori* in gastric mucosa involves various cellular signaling pathways associated with metabolic regulation, providing directions for novel therapeutic strategies.

GC induced by *H. pylori* is associated with chronic inflammation, characterized by neutrophil and macrophage infiltration in gastric epithelial cells, which facilitates the accumulation of pro-inflammatory cytokines and reactive ROS (47). The release of the virulence factor CagA upon infection activates downstream pathways, including and cytokine-stimulated transduction JAK-STAT signaling (48). This activation triggers expression of insulin growth factor (IGF)-1 and inflammatory pathways, further enhanced by cytokines such as IL-8, IL-1β, IL-6 and TNF-α (49).

H. pylori induces NADPH oxidase activation, producing ROS that activate NF-κB and Jak1-Stat3 pathways in gastric epithelial cells (13). Jak1-Stat3 activation serves as an upstream signal for NF-κB activation, inducing IL-8 expression in *H. pylori*-infected gastric cells (50). IL-8 transcription requires NF-κB activation, which is essential for the observed increase in IL-8 mRNA in infected cells (51).

Additionally, elevated serum IGF-1 levels, combined with *H. pylori* infection, may increase GC risk, *H. pylori*-induced PI3K/Akt/mTOR signaling regulates glycolysis and protein synthesis, supporting cellular growth and metabolism (52). Both *H. pylori* and IGF-1 activate the PI3K/Akt-mTOR pathway (49). The insulin pathway interacts with two tyrosine kinase receptors activated by insulin, IGF-1 and IGF-2 (18).

Insulin receptors (IRs) for IGF-1 and IGF-2 are highly expressed in GC cells (53,54). Exogenous IGF-1 and IGF-2 markedly stimulate GC cell proliferation and trigger downstream responses within the insulin pathway. Upregulation of IGF-1R may activate the PI3K/AKT/mTOR signaling cascade, promoting GC cell migration and invasion (49,55). Conversely, downregulating IGF-1 expression may disrupt IGF-1/IGF-2-IGF-1R signaling, inhibiting GC cell proliferation and invasion (56).

Hyperglycemia often coincides with insulin resistance and excessive activation of insulin signaling pathways may contribute to GC development. Insulin resistance can stimulate inflammatory responses and activate NF-κB, carrying out a key role in GC occurrence and progression (57). Hyperinsulinemia is associated with an increased incidence of GC and associates with elevated expression levels of IR and IGF1R (57). Increased expression of IGF-1, induced by hyperinsulinemia, acts as a mitogen, reducing apoptosis in tumor cells (22). IGF1-mediated signaling regulates multiple processes in GC (58), with interferon-induced transmembrane protein (IFITM)2, considered a tumor suppressor that is highly expressed in GC (58). The study indicated that IGF1R activation upregulates IFITM2 expression in GC and is associated with IL-6 secretion (58). STAT3, a transcription factor activated by IGF1/IGF1R signaling, carries out a key role in tumor progression (59) (Fig. 2); phosphorylated (p)-STAT3 is important in GC initiation and progression, promoting cell survival, proliferation, angiogenesis and metastasis (60,61). The IGF-2/IR-A signaling pathway has also been shown to notably promote malignancy in diabetic and prediabetic populations (62).

These results indicate an association between hyperglycemia and *H. pylori*-induced GC. The synergistic effect of hyperglycemia and *H. pylori* infection in GC development can be explained by hyperinsulinemia or insulin resistance. Hyperglycemia itself may act as a carcinogenic factor, excessive ROS production under hyperglycemic conditions leads to DNA strand breaks in nuclear or mitochondrial DNA, resulting in mutations of proto-oncogenes and tumor suppressor genes. Additionally, hyperglycemia-induced oxidative damage in the gastric mucosa may enhance the proliferative effects of *H. pylori* on epithelial cells, leading to genetic or epigenetic changes that promote GC development (24,63). A major feature of GC is altered glucose metabolism, with upregulated glycolysis requiring substantial glucose intake for cell proliferation and differentiation. Hyperglycemia promotes the growth and migration of cancer cells, facilitating GC progression (64).

3. TME

The TME is the cellular milieu in which tumor or cancer stem cells reside. The TME is a highly complex network composed of structurally and functionally essential elements in the typical matrix, including fibroblasts, myofibroblasts, neuroendocrine cells, immune and inflammatory cells, the blood and lymphatic vascular networks, and the extracellular matrix (ECM), which serves as a supportive framework (65). Due to the inherent proliferative characteristics of tumors, the TME provides a unique physicochemical environment and fosters complex metabolic patterns. The TME contains various cell types and secretory elements that can serve as potential targets for cancer therapy. Increasing evidence indicates that understanding the relationship between glucose metabolism and the TME represents a promising new direction for targeted therapies (66-69).

Role of the TME in GC. The acidic conditions and unique endocrine system in the stomach make the TME of GC distinct. Metabolites and cytokines secreted by these cell types, including GC cells, also constitute essential elements of the TME. Each component of the GC TME carries out a role in inducing immune tolerance, thereby promoting GC progression (70).

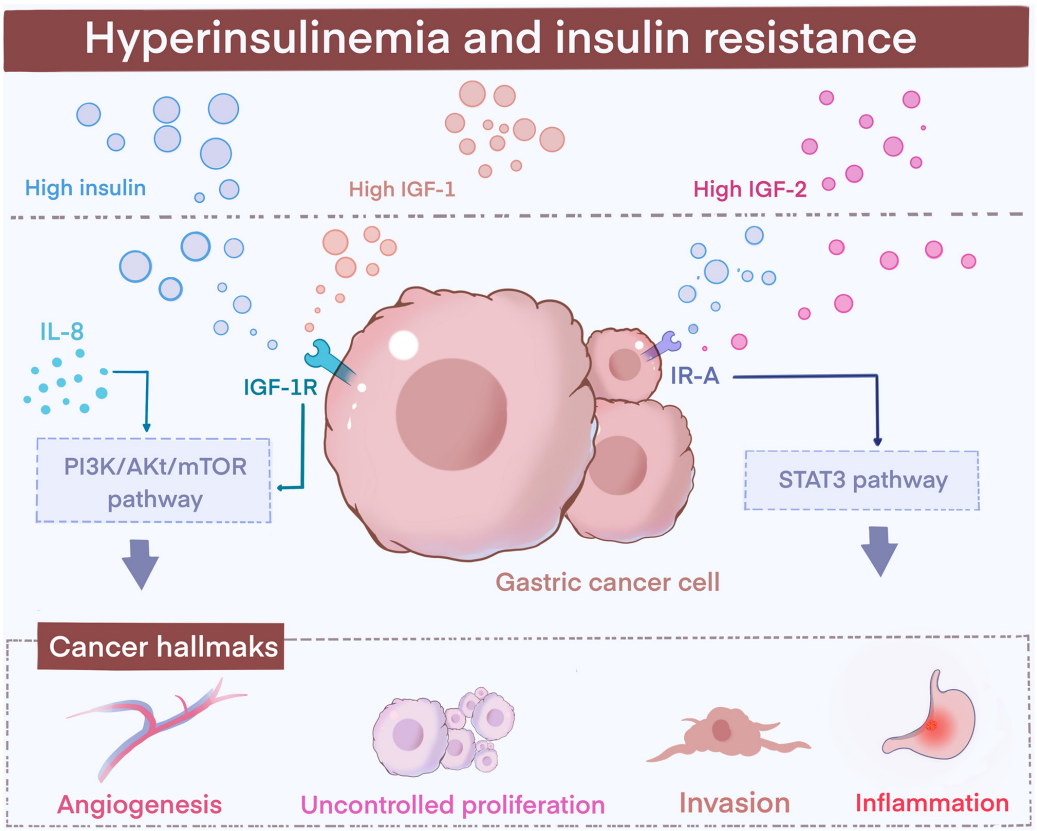

Figure 2. *H. pylori* infection under hyperglycemic conditions. *H. pylori* infection releases CagA and inflammatory cytokines (IL-8, IL-1β, IL-6 and TNF-α), activating IGF-1R-mediated PI3K/AKT/mTOR and IR-A/STAT3 pathways. Hyperinsulinemia elevates IGF-1/IGF-2 levels, further stimulating these cascades. Together, these signals promote glycolysis, proliferation, angiogenesis, invasion and chronic inflammation, reinforcing the Warburg effect in GC cells. Figure created using Procreate, Savage Interactive Pty Ltd (Version 5.4.7) and Adobe Illustrator, Adobe Inc 2025 (Version 29.x). *H. pylori*, *Helicobacter pylori*; CagA, Cytotoxin-associated gene A; GC, gastric cancer; IGF-1/2, insulin-like growth factor-1/2; IR-A, insulin receptor isoform A.

GC is associated with the TME. Typically, cancer cells exhibit dysregulated metabolism characterized by increased glucose consumption to fulfill anabolic demands. Emerging evidence indicates that cancer cell metabolism influences the immune status of the TME. When both the TCA cycle and glycolysis pathways are activated, the GC TME displays increased infiltration of anti-tumor effector cells, suggesting an enhancement in anti-tumor immune responses that may contribute to immune evasion and resistance to immunotherapy (71).

The TME is composed of diverse immune cells, including T lymphocytes, macrophages, NK cells and dendritic cells (72). Tumor-associated macrophages (TAMs), a notable TME component, substantially influence the interactions between cancer cells and their surroundings. TAMs exhibit notable functional plasticity, transforming into TAMs through reprogramming of monocytes that migrate to the tumor in response to recruitment signals. This transformation accelerates neovascularization and suppresses anti-tumor immune responses, promoting tumor growth, malignant transformation and invasiveness while diminishing anti-tumor T cell activity.

TAMs can be categorized into different subtypes based on functional states, mainly reflected in two polarization modes: M1 and M2. M1-polarized macrophages exhibit anti-cancer potential, producing pro-inflammatory cytokines such as IL-6, IL-8, IL-12 and TNF-α, which collectively inhibit tumor growth (65,66). Conversely, M2-polarized macrophages secrete anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, which are key for tumor progression, metastasis and angiogenesis, forming an essential component of the pro-tumorigenic microenvironment (73,74).

H. pylori may decrease M1 macrophage differentiation while promoting M2 macrophage differentiation or M1-to-M2 macrophage transdifferentiation, thereby facilitating tumor progression and invasion through the induction of angiogenesis in solid tumors and the mediation of immunosuppressive signals (75). In the early stages of GC, TAMs are recruited to the tumor site via chemokine signaling, contributing to tumor initiation. Notably, hypoxic environments enhance glycolytic pathways, which reduce the number of M1 macrophages, highlighting the role of metabolic reprogramming in the TME (76). The majority of TAMs adopt the M2 phenotype, which supports tumor expansion and metastasis by limiting antigen presentation and anti-tumor immune responses.

Studies indicate that TAMs compete with tumor cells within the TME for nutrients such as glucose (77,78). Carcinogenic and anti-cancer signals interact in this metabolic process, leading to glycolytic pathway activation and aerobic respiration inhibition. Glucose metabolism is regulated by various carcinogenic and tumor-suppressive signals, with activated glycolysis and impaired aerobic respiration shaping the altered glucose metabolism observed in GC (79). The acidic TME also profoundly affects TAM polarization. Lactic acid produced during high-glucose glycolysis intensifies TME acidification,

inducing TAM polarization towards the M2 phenotype and strengthening Treg function (80). Consequently, TAMs undergo glucose metabolism similar to that of tumor cells, contributing to metabolic reprogramming through activated glycolysis. Tumor progression may be hindered by reversing M2 TAM polarization back to the M1 state, thereby stimulating the immune system with pro-inflammatory characteristics (81).

TAMs secrete growth factors such as vascular endothelial growth factor and transform TGF-β, actively promoting vascular network formation and tissue structure remodeling. In advanced and metastatic GC, TAMs construct an immunosuppressive microenvironment through mechanisms that include T cell inhibition, regulatory Treg recruitment and the release of anti-inflammatory factors such as IL-10, IL-6 and TGF-β (82). These cumulative effects weaken the anti-cancer immune response of the host, leading to treatment resistance in advanced GC (83).

Adjacent to immune components, the metabolism of non-tumor cells in the TME also carries out a key role in cancer progression and treatment response. For instance, cancer-associated fibroblasts (CAFs) are primary components of the TME, secreting cytokines and ECM components that promote tumor cell proliferation, invasion and metastasis.

To survive under hypoxic tumor conditions, CAFs adopt a glycolytic metabolic pattern, supporting cancer cells by secreting growth factors and modifying the ECM, thereby undergoing metabolic reprogramming to meet TME demands. A study on secretomics revealed that *H. pylori* infection induces mesenchymal stem cell differentiation into CAF-like cells, reprogramming normal epithelial cells toward a pro-tumorigenic, invasive phenotype through an EMT associated with cancer stem cells (84). This transition disrupts cell junctions, enhances migration, reduces apoptosis and increases oncogenic potential.

TGF-β signaling in CAFs drives ECM remodeling and alters the physical properties of ECM fibers (82,85). Activation of TGF-β1/Smad2/3 signaling in CAFs upregulates glycolysis (86) (Fig. 3). Furthermore, ROS from cancer cells can induce oxidative stress in CAFs (87), leading to a metabolic shift from anaerobic respiration to glycolysis. This shift results in energy-rich metabolite production, including pyruvate, lactate and fatty acids, which nutritionally support other cancer cells (88).

CAFs secrete lactate, which tumors utilize for energy and intermediate products, a phenomenon known as the reverse Warburg effect (89). Lactate acts as both an energy source and a signaling molecule, underscoring the complexity of metabolic interactions within the TME. Understanding and targeting TME components holds potential for GC treatment, offering strategies to inhibit tumor growth and improve treatment efficacy.

Glucose metabolism in the TME. During growth, tumor cells adjust a range of metabolic processes to adapt to the nutrient-deprived TME, meeting the energy demands required for rapid proliferation. To support tumorigenesis and development, cells within the TME maintain a dynamic balance in interaction with cancer cells. As cancer cells proliferate abnormally, their oxygen demand sharply increases, triggering hypoxia and the formation of an acidic microenvironment within the tumor. In this context, the uncontrolled proliferation of tumor cells is closely associated with hypoxia and acidosis (8,90).

The study suggests that lactic acidosis can shift the predominant Warburg effect toward a non-glycolytic phenotype, suppressing glycolysis and enhancing mitochondrial respiration in cancer cells, potentially enabling cells to utilize glucose more efficiently in a metabolically restricted environment (91). Hypoxia not only directly influences tumor cell metabolic patterns but also disrupts the normal physiological structure of the gastric mucosa. Hypoxia is primarily mediated by HIFs, which enhance the 'Warburg effect' by upregulating glycolytic genes such as hexokinase, LDH-A and GLUT (92). In glycolysis, glucose or glycogen is broken down into pyruvate, ATP, NADH and lactate. Lactate, a byproduct of glycolysis, is present in the GC microenvironment and promotes macrophage polarization through HIF-1α-mediated angiogenic signals within the GC microenvironment (93). HIF-1 enhances glycolysis by promoting mitochondrial fission under hypoxic conditions, thereby facilitating malignant transformation of the gastric mucosa (94). These findings highlight the intricate and interdependent relationship between cancer cell metabolism and the TME.

4. *H. pylori* and glycolysis

H. pylori infection can lead to alterations in host metabolic reprogramming. In this section, unless otherwise specified, 'glycolysis' refers to aerobic glycolysis (Warburg effect) as defined in the Introduction. Glycolysis (commonly referred to as the Warburg effect in tumor metabolism) is a cellular phenomenon, which is also a key indicator of tumor progression, and there is an association between glycolysis and GC (95). The Warburg effect confers various survival advantages to cancer cells and markedly impacts the metabolic state and functional regulation of neighboring cells within the TME. The majority of the energy needed for tumor cell proliferation is derived from glycolysis, which is the main driver of the Warburg effect (96).

Tumor cells utilize glycolysis, oxidative phosphorylation (OXPHOS) and fatty acid oxidation as energy sources, adapting to microenvironmental changes and ensuring survival through metabolic reprogramming (97). *H. pylori*-induced glycolytic abnormalities not only increase energy consumption in host cells but also promote cytokine release and inflammatory responses. The elevated glycolytic rate provides a rich nutrient source for the bacteria, exacerbating gastric mucosal damage and establishing a vicious cycle. Consequently, targeting the glycolytic pathway has emerged as a novel strategy for treating *H. pylori* infection.

Characterization of glycolysis in GC. In normal, differentiated cells, OXPHOS serves as the primary energy pathway. Mitochondria are the main site of cellular OXPHOS, where NADH and $FADH_2$ transfer electrons to oxygen through the electron transport chain (ETC), generating a proton gradient that drives ATP synthase to produce ATP, the most efficient cellular energy production method (8). By contrast, tumor cells exhibit a marked preference for glycolysis, even in oxygen-rich conditions, displaying a high capacity for glucose uptake and lactate accumulation. This metabolic shift is considered an adaptive response to the high energy demands of rapidly

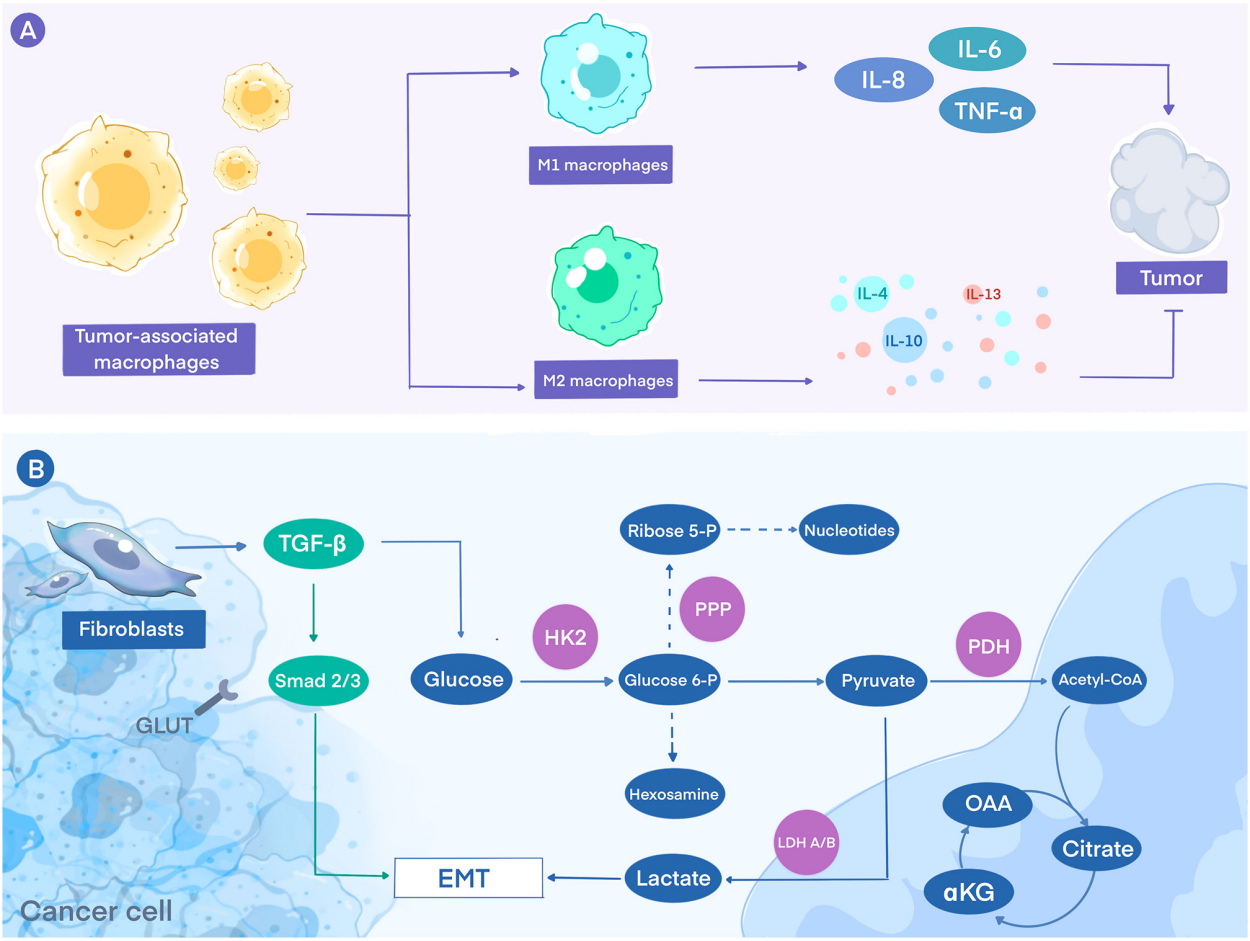

Figure 3. TME regulated by *H. pylori* infection. (A) The polarization of macrophages into M1 and M2 phenotypes, which is influenced by hypoxia inducible factor-1 and lactic acid. M1 macrophages produce pro-inflammatory cytokines, including IL-6, IL-8 and TNF-α, which contribute to anti-tumor immunity. By contrast, M2 macrophages secrete anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, promoting tumor growth and immune evasion. (B) Glycolytic Pathway Alterations in *H. pylori*-Associated GC Cells. CAFs positioned in the tumor microenvironment secrete TGF-β, which activates Smad 2/3 signaling in GC cells. This signaling enhances HK2-mediated glycolysis, leading to increased production of glucose-6-phosphate, diversion into the PPP for ribose-5-phosphate and nucleotide synthesis, and conversion to lactate via LDH-A/B. Lactate is exported from CAFs or cancer cells, acidifying the microenvironment and promoting EMT. Meanwhile, pyruvate generated during glycolysis enters the TCA cycle through PDH, producing acetyl-CoA, citrate, OAA and αKG. This schematic illustrates the metabolic cross-talk between *H. pylori*-associated GC cells and CAFs, highlighting how stromal-derived signaling and metabolites reinforce tumor glycolysis and biosynthetic activity within the 'reverse Warburg effect' framework. Figure created using Procreate (Version 5.4.7); Savage Interactive Pty Ltd and Adobe Illustrator, Adobe Inc 2025 (Version 29.x). *H. pylori*, *Helicobacter pylori*. GC, gastric cancer; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor-β; HK2, Hexokinase 2; Glucose 6-P, Glucose-6-Phosphate; PPP, pentose phosphate pathway; PDH, pyruvate dehydrogenase; EMT, epithelial-mesenchymal transition; LDH A/B, lactate dehydrogenase A/B; OAA, oxaloacetate; αKG, α-ketoglutarate.

proliferating tumor cells, enabling cancer cells to meet their metabolic requirements during rapid growth (98,99).

Under aerobic conditions, GC cells exhibit abnormal metabolic characteristics, primarily converting pyruvate to lactate. Although this process is less efficient in terms of ATP production, it effectively generates the intermediate metabolites necessary for rapid cell proliferation, resulting in a proliferation rate distinct from that of normal cells. Additionally, lactate is the final product of the Warburg effect, and its accumulation during glycolysis creates an acidic environment that destabilizes the extracellular matrix, promoting tumor cell metastasis. Lactate can also facilitate immune evasion by directly inhibiting the cytotoxicity and proliferation of immune cells (100).

H. pylori is a primary factor in GC development The study indicates that it promotes GC by enhancing glycolysis and inducing mitochondrial dysfunction (101). Mitochondrial functional defects often result from elevated ROS levels during mitochondrial electron transport, which halts OXPHOS and promotes a switch to glycolysis in tumor cells (102). This abnormal mitochondrial metabolic pattern supplies the tumor with a steady flow of nutrients and adaptability, enabling cancer cells to survive and proliferate rapidly. The underlying mechanisms involve the reversibility of several reactions within the TCA cycle and the presence of multiple anaerobic pathways centered around mitochondria, which ensure metabolic flexibility (103,104). The Warburg effect facilitates efficient energy acquisition in tumor cells through glycolysis and lactic acid fermentation, providing a metabolic advantage conducive to growth and proliferation. Meanwhile, mitochondrial metabolism remains essential for sustained tumor growth, coordinating the TCA cycle and ETC to offer a stable biosynthetic source for tumor cells.

Challenges and clinical considerations in targeting glycolysis for cancer therapy. Although inhibition of glycolysis has emerged as a promising anti-cancer strategy, multiple

challenges hinder its clinical translation. Metabolic plasticity in tumors allows cancer cells to adapt to glycolytic blockade by switching to alternative energy pathways, such as oxidative phosphorylation or glutaminolysis, thereby reducing the efficacy of therapy (105,106). Glycolysis is also indispensable for certain normal rapidly proliferating cells, including activated immune cells, raising concerns regarding systemic toxicity when it is broadly inhibited (107). Moreover, marked metabolic heterogeneity exists both among tumor types and within distinct intratumoral regions; hypoxic areas rely predominantly on glycolysis, whereas normoxic regions favor oxidative metabolism, making uniform targeting less effective (96,108). Prolonged inhibition of glycolysis may activate compensatory signaling networks and induce metabolic reprogramming, resulting in acquired drug resistance (109).

Despite these challenges, the dependence of *H. pylori*-associated GC on specific glycolytic enzymes such as HK2, PKM2, LDHA and PDK1 presents actionable vulnerabilities. The following section provides a comprehensive overview of these glycolysis-related therapeutic targets, summarizing their regulatory mechanisms, prognostic relevance and current pharmacological strategies, including synthetic inhibitors, repurposed drugs and phytochemicals, to guide future translational research.

Association between the expression of glycolysis-related enzymes and the prognosis of GC. The Warburg effect can enhance the expression of key glycolytic enzymes such as hexokinase (HK), glucose transporter (GLUT), lactate dehydrogenase (LDH), pyruvate kinase (PK) and 3-phosphoinositide-dependent protein kinase 1 (PDK1), increasing tumor cell tolerance to hypoxic conditions and promoting the invasion and metastasis of malignancies (95). Therefore, the state of glycolysis may also serve as a potential biomarker for cancer prognosis.

HK2 carries out a central role in the Warburg effect and the development of malignant tumors. As a downstream effector of Akt in cancerous environments, HK2 exhibits a high affinity for glucose (110). HK2 is anchored to the outer mitochondrial membrane through its interaction with the mitochondrial protein voltage-dependent anion channel (VDAC), shielding it from inhibition by glucose-6-phosphate, the end product of its catalysis. This anchoring markedly increases the glycolysis rate, enhancing ATP production efficiency (111).

The ample ATP supplied by mitochondria accelerates HK2-catalyzed, rate-limiting steps in glycolysis. During *H. pylori* infection, dysregulation of glycolysis in the gastric mucosa is observed, Immunohistochemistry analyses confirmed elevated HK2 expression in patients infected with *H. pylori*, with markedly increased levels observed in the gastric mucosa (112,113).

Hexokinase domain-containing 1 (HKDC1) is involved in mediating aerobic glycolysis and contributes to tumorigenesis in various types of cancer. In *H. pylori*-induced GC, *H. pylori* modulates the EMT pathway by upregulating TGF-β1 expression via HKDC1. *In vitro* and *in vivo* experiments demonstrated that *H. pylori* infection increases the expression of TGF-β1 and p-Smad2, thereby activating the EMT pathway, whereas HK1 and HK2, which are mitochondrial-associated proteins, exhibit an upward trend in expression (113). Current eradication therapies still rely mainly on proton pump inhibitors (PPIs) and antibiotics. Rabeprazole, a second-generation PPI commonly used in peptic ulcer treatment, has been shown to exert effects beyond acid suppression. As demonstrated by Zhou *et al* (112), rabeprazole suppresses STAT3 phosphorylation and nuclear translocation, thereby reducing STAT3 binding to the HK2 promoter and downregulating HK2 transcription. Furthermore, direct metabolic intervention represents another strategic approach. Notably, thyroid hormone T3 therapy can drive a metabolic shift from HK2-driven glycolysis to mitochondrial OXPHOS, which has been demonstrated to inhibit tumor development (101). The HK2 inhibitor 3-bromopyruvate and the phosphofructokinase inhibitor sodium citrate suppress glycolysis and promote mitochondrial-associated apoptosis in GC through the downregulation of the anti-apoptotic protein Bcl-2 and the upregulation of the pro-apoptotic protein Bax (114). Consequently, these agents markedly inhibit tumor cell proliferation and glycolytic activity in orthotopic xenograft models of GC. Together, these findings underscore the broad potential of targeting cellular metabolism, positioning the STAT3/HK2 axis and glycolytic pathway as promising targets for improving the prognosis of patients infected with *H. pylori* (115).

The PI3K/Akt signaling pathway, one of the commonly dysregulated pathways in tumors, extensively regulates cellular metabolic reprogramming by upregulating glucose transporters and glycolytic enzymes. Cellular glucose uptake largely depends on membrane transporter concentration, mainly by the glucose transporter family, with GLUT1 being a key rate-limiting step in glucose uptake (116). GLUT1 is highly expressed in primary GC and is associated with disease stage and prognosis, suggesting its role in glucose homeostasis in GC cells (116,117). During *H. pylori* infection, HIF-1α and bromodomain-containing protein 4 (BRD4) cooperate to increase glycolysis by transcriptionally activating GLUT1 and HK2. BRD4 deficiency reduces HIF-1α-dependent GLUT1 expression and HK2 levels, thereby impairing glucose uptake and glycolytic capacity (118). By targeting Na^+/K^+-ATPase, cardiac glycosides (CGs), including ouabain, oleandrin and digoxin, inhibit glycolytic metabolism in GC cells. In MKN45 cells, CGs downregulate plasma membrane GLUT1 expression, with ouabain being effective at sub-inhibitory concentrations for the α1 subunit. This leads to suppressed 2-deoxy-D-glucose uptake, decreased lactate production and impaired cell proliferation (119). Therefore, GLUT1 may serve as a potential therapeutic target for GC.

LDHA, a key glycolytic enzyme, converts pyruvate to lactate and is overexpressed in gastrointestinal tumors, particularly GC. GC cells rely on high GLUT expression for increased glucose uptake and energy metabolism. Lactic acid accumulation in GC cells promotes glucose metabolism and glycolysis rates and enhances cancer progression and invasiveness by inducing histone lactylation (120). In GC, LDHA is markedly upregulated by transcription factors such as HIF-1α and c-Myc. This enhanced expression promotes the conversion of pyruvate to lactate, which not only sustains high glycolytic flux by regenerating NAD^+ but also results in lactate accumulation, thereby fostering an acidic TME. High LDH expression is a key factor in the development of GC. A proteomics study revealed that *H. pylori* infection promotes the expression of this gene in GC tissues (121). These changes collectively enhance tumor cell proliferation, invasion and

immune evasion. Targeting this metabolic pathway with LDH-A inhibitors has emerged as a promising therapeutic strategy. Among them, oxamate, a well-established LDH inhibitor and pyruvate analog, competitively binds to the catalytic site of LDH-A, thereby blocking pyruvate-to-lactate conversion, impairing NAD^+ regeneration, and ultimately leading to suppressed glycolysis, reduced ATP production and apoptosis induction (122). In a distinct manner, silibinin, a polyphenolic compound derived from Silybum marianum, impedes glycolytic metabolism by inhibiting the HIF-1α/LDH-A axis, thereby enhancing antitumor immune responses (123-126). Both compounds represent promising candidates for anticancer therapy through targeting glycolysis. 5-FU-resistant GC cells show enhanced glycolysis, along with upregulation of key glycolytic enzymes such as HK2 and LDHA. CagA activates the Akt pathway, enhancing glycolysis in GC cells and leading to 5-FU resistance. Inhibiting glycolysis or the Akt pathway can overcome this resistance (127).

The expression of PKM2, a glycolysis-related enzyme associated with tumor progression, is upregulated in GC cells due to CagA, which induces increased PKM2 expression and increases with GC progression. PKM2 has been shown to regulate cancer-specific metabolic pathways that drive gastric cancer cell proliferation and tumor growth by enhancing glycolytic flux, highlighting its key role in metabolic reprogramming in GC (128). CagA promotes GC development by inducing PKM2 expression via the Erk pathway. Furthermore, PKM2 carries out an essential role in regulating the final stage of glycolysis, facilitating glycolysis in cancer cells by catalyzing the transfer of a phosphate group from phosphoenolpyruvate to ADP, forming ATP and pyruvate (129). At present, there is no direct evidence supporting an association between PKM2 and *H. pylori* infection. Shikonin, a natural product derived from the roots of medicinal herbs such as *Lithospermum erythrorhizon, Arnebia euchroma and Onosma paniculata,* exerts anticancer effects partly through suppression of glycolysis in tumor cells. Its mechanism involves the inhibition of PKM2 phosphorylation, thereby reducing PKM2 activity. This finding is supported by evidence that both PKM2 inhibitors and activators can alter the effect of shikonin on glycolysis (130). The PI3K/Akt/mTOR signaling pathway, which is known to regulate cell proliferation, apoptosis and glucose metabolism, appears to be relevant in this context. For instance, the specific PI3K inhibitor LY294002 has been shown to suppress GC cell proliferation, induce early apoptosis and markedly reduce lactate dehydrogenase activity and lactate production, effects partly attributed to the inhibition of PKM2 expression (131,132). Downregulation of PKM2 subsequently decreased the expression of Glut-1 and LDHA, attenuating the Warburg effect. In parallel, pantoprazole (PPZ), a third-generation proton pump inhibitor identified as a PKM2 inhibitor, suppresses the Akt/GSK-3β/β-catenin pathway and restores chemosensitivity in GC cells (101,133). PPZ also reverses chemoresistance in SGC7901 cells by downregulating V-ATPase/mTOR/HIF-1α-mediated P-gp and MRP1 signaling. Collectively, these findings highlight PKM2 as a promising target for metabolic intervention in GC.

PDK-1 is a key enzyme that reduces mitochondrial ROS. It acts as a direct target of HIF-1α. PDK-1 blocks the conversion of pyruvate to acetyl-CoA, thereby preventing pyruvate from entering the TCA cycle and inhibiting its metabolism within the cycle. This shift, regulated by HIF-1α-targeted PDK-1, from aerobic oxidation to glycolytic glucose metabolism, reduces mitochondrial oxygen consumption and limits ROS accumulation, ultimately promoting tumor growth (93). *H. pylori* infection induces PDK1 dephosphorylation, resulting in aberrant Akt phosphorylation and degradation, which disrupts cell survival signaling and the balance between apoptosis and proliferation. In CagA-positive-GC cells, inhibition of Akt phosphorylation or key glycolytic enzymes (HK2/LDHA) synergistically enhances the cytotoxicity of 5-FU and markedly reverses drug resistance (105). *In vitro* data indicate that high PDK1 expression in GC cells is associated with reduced sensitivity to 5-FU, suggesting that PDK1 overexpression is a potential marker of poor prognosis (134,135). In gastric AGS cells, *H. pylori* infection leads to PDK-1 dephosphorylation, which disrupts cyclic PI3K signaling pathways related to cell survival post-infection. This dephosphorylation of PDK-1, along with changes in Akt phosphorylation, is one of the mechanisms by which *H. pylori* infection alters the balance between apoptosis and cell proliferation, potentially contributing to *H. pylori*-induced GC development (136). Dichloroacetate (DCA), a non-specific mitochondrial PDK-1 inhibitor, has been demonstrated to reactivate pyruvate dehydrogenase, thereby shifting pyruvate metabolism from glycolysis toward mitochondrial oxidative phosphorylation and subsequently suppressing lactate production. This metabolic reprogramming not only disrupts glycolytic flux but also may enhance cancer cell sensitivity to conventional therapies (137,138). On the basis of this evidence, the present review reviewed published studies and evaluated the effects of DCA monotherapy alone and in combination with 5-FU in GC cell lines exhibiting high PDK-1 expression and elevated glycolytic activity. Hur *et al* (135) were the first to demonstrate that low-dose DCA induces marked metabolic alterations in these PDK-1-overexpressing cells with minimal effects on cell viability. Therefore, the observed synergistic effect between DCA and 5-FU suggests that DCA could serve as a promising adjunctive agent to conventional chemotherapy, particularly for patients with treatment-resistant disease and poor prognosis.

5. Comprehensive overview of glycolysis-related therapeutic targets

To the best of our knowledge, research on the use of various molecules associated with abnormal glucose metabolism as prognostic biomarkers in GC is limited. Furthermore, the therapeutic potential of drugs targeting glycolysis for treating GC remains largely unexplored. The present review systematically synthesized published studies on agents targeting glucose metabolism in human GC cell lines and summarized their reported efficacy, offering a novel perspective for GC treatment. *H. pylori* infection reprograms gastric cell metabolism toward enhanced glycolysis, markedly upregulating HK2, PKM2, LDHA and PDK1 expression. These alterations, driven by inflammation and hypoxia-related signaling, promote tumor progression and represent promising therapeutic targets.

In addition to synthetic inhibitors and repurposed drugs such as 2-deoxy-D-glucose and rabeprazole, several plant-derived phytochemicals have demonstrated notable glycolysis-inhibiting activity in GC models, offering multi-target modulation

Table I. Key glycolytic enzymes as potential therapeutic targets in *H. pylori*-associated GC.

Glycolytic enzyme and target	Expression and regulation in *H. pylori*-related GC	Therapeutic strategy/specific drugs	Mechanism of action	Current research stage/clinical evidence	(Refs.)
HK2	Infection with *H. pylori* activates the PI3K/Akt/mTOR signaling pathway, which increases HIF-1α expression and consequently upregulates HK2. NF-κB-mediated inflammatory signaling also enhances HK2 expression, promoting glycolysis and inhibiting apoptosis.	Chemical inhibitors: 2-DG, 3-BrPA, SCT13; repurposed drugs: Rabeprazole, Noradrenaline, T3; natural compounds: Licochalcone A, Baicalein, Curcumin, Resveratrol, Quercetin.	Inhibition of HK2 decreases the formation of glucose-6-phosphate, which reduces ATP and lactate production and induces apoptosis. Rabeprazole blocks STAT3 phosphorylation, thereby decreasing HK2 transcription. Natural compounds inhibit the Akt/mTOR/HIF-1α axis, which leads to decreased HK2 expression.	2-DG: Phase I/II trial in advanced solid tumors (NCT00096707); Rabeprazole-preclinical GC models.	(101,110,111, 127,139,140, 143-148, 152-154)
PKM2	PKM2 is upregulated in GC, regulating metabolic pathways that support tumor growth. HIF-1α/c-Myc enhance PKM2 transcription, and PI3K/Akt/mTOR signaling promotes its nuclear localization.	Chemical inhibitors: Shikonin, TEPP-46; Repurposed drugs: Pantoprazole, LY294002; natural compounds: Baicalein, Licochalcone A, Curcumin.	Inhibition of PKM2 blocks the conversion of PEP to pyruvate, which suppresses glycolysis. Pantoprazole reduces Akt/GSK-3β/β-catenin signaling, leading to decreased PKM2 expression.	Preclinical; controversy on PKM2's non-metabolic nuclear functions in tumor regulation.	(127,130,131, 133,139,140, 144,145)
LDHA	HIF-1α together with c-Myc increases LDHA expression, leading to elevated lactate production and acidification of the tumor microenvironment.	Chemical inhibitors: Oxamate, FX11; repurposed drugs: Natural compounds: Silibinin, Licochalcone A, Baicalein, Curcumin, Resveratrol, EGCG, Quercetin, Noradrenaline.	Inhibition of LDHA reduces lactate accumulation and NAD^+ regeneration, resulting in decreased glycolytic flux. Silibinin inhibits the HIF-1α/LDHA axis, which lowers LDHA expression.	Oxamate, preclinical (murine models).	(122,123,126, 127,142,139, 144,145,149, 150)
PDK-1	*H. pylori*-induced HIF-1α expression upregulates PDK1, which inhibits PDH. This shifts metabolism toward increased lactate production and contributes to chemoresistance.	Chemical inhibitors: DCA; repurposed drugs: Natural compounds: Baicalein, Curcumin, Resveratrol, EGCG, Quercetin, Licochalcone A.	Inhibition of PDK1 reactivates PDH, facilitating entry of pyruvate into the TCA cycle. This reduces lactate production and increases chemosensitivity.	DCA: Phase I/II trials in glioblastoma (NCT00566410); limited trial data are available for GC.	(127,135, 137-139, 144,145,151, 155,156)

HK2, hexokinase 2; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; PDK1, pyruvate dehydrogenase kinase 1; TME, tumor microenvironment; PEP, phosphoenolpyruvate; PDH, pyruvate dehydrogenase; TCA cycle, tricarboxylic acid cycle; HIF-1α, hypoxia-inducible factor 1-α; EGCG, epigallocatechin gallate; 2-DG, 2-deoxy-D-glucose; 3-BrPA, 3-bromopyruvate; DCA, Dichloroacetate.

with generally favorable safety profiles. These natural compounds interfere with diverse oncogenic and metabolic signaling cascades, ultimately reducing lactate production and impairing tumor cell bioenergetics (139). Rosmarinic acid, a phenolic compound abundantly found in aromatic plants, suppresses glycolysis in GC cells by inhibiting the IL-6/STAT3 pathway (140). Curcumin, the main polyphenol in turmeric, downregulates HK2, PKM2 and LDHA expression via inhibition of the PI3K/Akt/mTOR and HIF-1α signaling pathways, leading to reduced lactate generation (141). Resveratrol, a stilbene found in grapes, diminishes HK2 and LDHA expression through inhibition of HIF-1α and c-Myc, and blocks GLUT1-mediated glucose uptake. Epigallocatechin gallate, the major catechin in green tea, targets both GLUT1 and LDHA, thereby suppressing lactate production and increasing oxidative metabolism (142). Quercetin, a flavonoid widely distributed in edible plants, interferes with the Akt/mTOR pathway, resulting in decreased glycolytic enzyme activity and reduced lactate levels (127). These alterations, driven by inflammation- and hypoxia-related signaling, promote tumor progression and represent promising therapeutic targets. Table I (101,110,111,122,123,126,127,130,131,133,135,137-140,142-156) summarizes their regulation, prognostic significance, representative inhibitors, mechanisms of action and current development status, providing a concise reference for future translational research.

6. Summary and future research directions

H. pylori infection drives gastric carcinogenesis by inducing a profound metabolic shift toward glycolysis (the Warburg effect). Mechanistically, virulence factors activate oncogenic signaling, including the PI3K/Akt/mTOR and STAT3 pathways. These pathways converge on the level of the transcription factor HIF-1α, which upregulates key glycolytic enzymes such as HK2, PKM2 and LDHA. This metabolic reprogramming provides the bioenergetic and biosynthetic substrates essential for cell proliferation, survival and invasion.

This reliance on glycolysis, however, represents a key therapeutic vulnerability. 2-Deoxy-D-glucose (2-DG), a glycolysis inhibitor studied since the late 1950s, showed limited effects in early monotherapy trials, indicating that cancer cells can metabolize alternative substrates via oxidative phosphorylation. In the first trial combining 2-DG with weekly docetaxel (NCT00096707), the regimen was well tolerated without pharmacokinetic interaction, achieving disease control in 32% of 34 patients (1 partial response; 11 stable disease ≥8 weeks). Preclinical evidence of enhanced chemotherapy cytotoxicity supports further Phase II evaluation (152). Preclinical evidence has indicated DCA can reverse the Warburg effect and inhibit tumor growth in cancer models. In the clinical setting, a Phase I/II trial in recurrent glioblastoma (NCT00566410) explored positron emission tomography (PET) scanning using 18F-FDG uptake as a potential biomarker of response; in some patients, prolonged DCA administration was associated with stable tumor size and reduced 18F-FDG uptake. Given its non-cytotoxic mechanism and slow onset of action, the preclinical study suggests that DCA may be more effective as an apoptosis-sensitizer in combination with cytotoxic or targeted therapies compared with as monotherapy (156). Furthermore, the identification of predictive biomarkers, such as the expression levels of key glycolytic enzymes, is key for patient stratification and the development of a precision medicine approach for *H. pylori*-associated GC.

Acknowledgements

Not applicable.

Funding

Research grants were provided by the National Natural Science Foundation of China (grant nos. 82170628, 32160208, 82560124, and 82570604), the Science and Technology Plan Project of Guizhou Province [grant no. QIAN KE HE JI CHU-ZK (2023) YI BAN 556] and the Guizhou Provincial Department of Science and Technology [grant no. QIAN KE HE PING TAI REN CAI-GCC (2023) 040].

Availability of data and materials

Not applicable.

Authors' contributions

YL, FW, YD, YH, FS, JY, GG, MW, CL, XL, QD, JX and RX contributed to conceiving the review; acquiring and analyzing data; drafting, reviewing, revising and approving the manuscript; and the decision to submit it for publication. No datasets were generated or analyzed for the present study. Data authentication not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA and Bray F: Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 159: 335-349.e15, 2020.
3. Zhou Y, Song K, Chen Y, Zhang Y, Dai M, Wu D and Chen H: Burden of six major types of digestive system cancers globally and in China. Chin Med J (Engl) 137: 1957-1964, 2024.
4. Sexton RE, Al Hallak MN, Diab M and Azmi AS: Gastric cancer: A comprehensive review of current and future treatment strategies. Cancer Metastasis Rev 39: 1179-1203, 2020.
5. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R and Polkowski WP: Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Manag Res 10: 239-248, 2018.

6. Niu P, Zhang F, Ma D, Zhou X, Zhu Y, Luan X, Zhao L, Wang W, Zhang X, Han X, *et al*: Trends of older gastric cancer incidence, mortality, and survival in the highest gastric cancer risk area in China: 2010-2019 and prediction to 2024. BMC Public Health 24: 2449, 2024.
7. Wu Y, Ma W, Liu W and Zhang S: Lactate: A pearl dropped in the ocean: An overlooked signal molecule in physiology and pathology. Cell Biol Int 47: 295-307, 2023.
8. Barba I, Carrillo-Bosch L and Seoane J: Targeting the warburg effect in cancer: Where do we stand? Int J Mol Sci 25: 3142, 2024.
9. Paul S, Ghosh S and Kumar S: Tumor glycolysis, an essential sweet tooth of tumor cells. Semin Cancer Biol 86: 1216-1230, 2022.
10. Shima T, Taniguchi K, Inomata Y, Arima J and Lee SW: Glycolysis in gastrointestinal stromal tumor: A brief overview. Neoplasia 55: 101022, 2024.
11. Xia Y, Zhang L, Ocansey DKW, Tu Q, Mao F and Sheng X: Role of glycolysis in inflammatory bowel disease and its associated colorectal cancer. Front Endocrinol (Lausanne) 14: 1242991, 2023.
12. Wang F, Meng W, Wang B and Qiao L: *Helicobacter pylori*-induced gastric inflammation and gastric cancer. Cancer Lett 345: 196-202, 2014.
13. Cha B, Lim JW and Kim H: Jak1/Stat3 is an upstream signaling of NF-κB activation in *Helicobacter pylori*-induced IL-8 production in gastric epithelial AGS cells. Yonsei Med J 56: 862-866, 2015.
14. Salvatori S, Marafini I, Laudisi F, Monteleone G and Stolfi C: *Helicobacter pylori* and gastric cancer: Pathogenetic mechanisms. Int J Mol Sci 24: 2895, 2023.
15. Yang SW, Kwon HS, Sohn IS, Kim YJ and Hwang HS: Association of Vac A- and Cag A-specific *Helicobacter pylori* strain infection with spontaneous preterm birth. J Matern Fetal Neonatal Med 30: 995-1000, 2017.
16. D'Elios MM, Manghetti M, De Carli M, Costa F, Baldari CT, Burroni D, Telford JL, Romagnani S and Del Prete G: T helper 1 effector cells specific for *Helicobacter pylori* in the gastric antrum of patients with peptic ulcer disease. J Immunol 158: 962-967, 1997.
17. Kang GH, Lee HJ, Hwang KS, Lee S, Kim JH and Kim JS: Aberrant CpG island hypermethylation of chronic gastritis, in relation to aging, gender, intestinal metaplasia, and chronic inflammation. Am J Pathol 163: 1551-1556, 2003.
18. Kwon HJ, Park MI, Park SJ, Moon W, Kim SE, Kim JH, Choi YJ and Lee SK: Insulin resistance is associated with early gastric cancer: A prospective multicenter case control study. Gut Liver 13: 154-160, 2019.
19. Noto JM, Piazuelo MB, Romero-Gallo J, Delgado AG, Suarez G, Akritidou K, Girod Hoffman M, Roa JC, Taylor CT and Peek RM Jr: Targeting hypoxia-inducible factor-1 alpha suppresses *Helicobacter pylori*-induced gastric injury via attenuation of both cag-mediated microbial virulence and proinflammatory host responses. Gut Microbes 15: 2263936, 2023.
20. Zhang M, Zhong J, Song Z, Xu Q, Chen Y and Zhang Z: Regulatory mechanisms and potential therapeutic targets in precancerous lesions of gastric cancer: A comprehensive review. Biomed Pharmacother 177: 117068, 2024.
21. Canales J, Valenzuela M, Bravo J, Cerda-Opazo P, Jorquera C, Toledo H, Bravo D and Quest AF: *Helicobacter pylori* induced phosphatidylinositol-3-OH kinase/mTOR activation increases hypoxia inducible factor-1α to promote loss of cyclin D1 and G0/G1 cell cycle arrest in human gastric cells. Front Cell Infect Microbiol 7: 92, 2017.
22. Wang L and Zhang Z: Diabetes mellitus and gastric cancer: Correlation and potential mechanisms. J Diabetes Res 2023: 4388437, 2023.
23. Sheu SM, Cheng H, Kao CY, Yang YJ, Wu JJ and Sheu BS: Higher glucose level can enhance the H pylori adhesion and virulence related with type IV secretion system in AGS cells. J Biomed Sci 21: 96, 2014.
24. Ikeda F, Doi Y, Yonemoto K, Ninomiya T, Kubo M, Shikata K, Hata J, Tanizaki Y, Matsumoto T, Iida M and Kiyohara Y: Hyperglycemia increases risk of gastric cancer posed by *Helicobacter pylori* infection: A population-based cohort study. Gastroenterology 136: 1234-1241, 2009.
25. Ahn BY, Kim B, Park S, Kim SG, Han K and Cho SJ: Cumulative exposure to impaired fasting glucose and gastrointestinal cancer risk: A nationwide cohort study. Cancer 130: 1807-1015, 2024.
26. Tseng CH: The relationship between diabetes mellitus and gastric cancer and the potential benefits of metformin: An extensive review of the literature. Biomolecules 11: 1022, 2021.
27. Mansori K, Dehghanbanadaki H, Naderpour S, Rashti R, Moghaddam AB and Moradi Y: A systematic review and meta-analysis of the prevalence of *Helicobacter pylori* in patients with diabetes. Diabetes Metab Syndr 14: 601-607, 2020.
28. Grant RW, Buse JB and Meigs JB; University HealthSystem Consortium (UHC) Diabetes Benchmarking Project Team: Quality of diabetes care in U.S. academic medical centers: Low rates of medical regimen change. Diabetes Care 28: 337-442, 2005.
29. Wang X, Zhao G, Shao S and Yao Y: *Helicobacter pylori* triggers inflammation and oncogenic transformation by perturbing the immune microenvironment. Biochim Biophys Acta Rev Cancer 1879: 189139, 2024.
30. Walduck A, Andersen LP and Raghavan S: Inflammation, immunity, and vaccines for *Helicobacter pylori* infection. Helicobacter 20 (Suppl 1): S17-S25, 2015.
31. Yang XT, Niu PQ, Li XF, Sun MM, Wei W, Chen YQ and Zheng JY: Differential cytokine expression in gastric tissues highlights *Helicobacter pylori*'s role in gastritis. Sci Rep 14: 7683, 2024.
32. Shoelson SE, Herrero L and Naaz A: Obesity, inflammation, and insulin resistance. Gastroenterology 132: 2169-2180, 2007.
33. Chen B, Liu X, Yu P, Xie F, Kwan JSH, Chan WN, Fang C, Zhang J, Cheung AHK, Chow C, *et al*: H: pylori-induced NF-κB-PIEZO1-YAP1-CTGF axis drives gastric cancer progression and cancer-associated fibroblast-mediated tumour microenvironment remodelling. Clin Transl Med 13: e1481, 2023.
34. Gong P, Wang J, Wang S, Yang W, Yao W, Li N, Wang J, Zhao Y, Chen F, Xie J, *et al*: Metabolomic analysis of the Puerarin hypoglycemic activity via AMPK-mTOR and PPARγ-NF-κB signaling pathways. Phytomedicine 130: 155546, 2024.
35. Yu H, Lin L, Zhang Z, Zhang H and Hu H: Targeting NF-κB pathway for the therapy of diseases: Mechanism and clinical study. Signal Transduct Target Ther 5: 209, 2020.
36. de Lima EP, Moretti RC Jr, Torres Pomini K, Laurindo LF, Sloan KP, Sloan LA, Castro MVM, Baldi E Jr, Ferraz BFR, de Souza Bast os Mazuqueli Pereira E, *et al*: Glycolipid metabolic disorders, metainflammation, oxidative stress, and cardiovascular diseases: Unraveling pathways. Biology (Basel) 13: 519, 2024.
37. Espinoza García AS, Martínez Moreno AG and Reyes Castillo Z: The role of ghrelin and leptin in feeding behavior: Genetic and molecular evidence. Endocrinol Diabetes Nutr (Engl Ed) 68: 654-663, 2021.
38. Khosravi Y, Bunte RM, Chiow KH, Tan TL, Wong WY, Poh QH, Doli Sentosa IM, Seow SW, Amoyo AA, Pettersson S, *et al*: *Helicobacter pylori* and gut microbiota modulate energy homeostasis prior to inducing histopathological changes in mice. Gut Microbes 7: 48-53, 2016.
39. Roper J, Francois F, Shue PL, Mourad MS, Pei Z, Olivares de Perez AZ, Perez-Perez GI, Tseng CH and Blaser MJ: Leptin and ghrelin in relation to *Helicobacter pylori* status in adult males. J Clin Endocrinol Metab 93: 2350-2357, 2008.
40. Franceschi F, Annalisa T, Teresa DR, Giovanna D, Ianiro G, Franco S, Viviana G, Valentina T, Riccardo LL and Antonio G: Role of *Helicobacter pylori* infection on nutrition and metabolism. World J Gastroenterol 20: 12809-12817, 2014.
41. Açbay O, Celik AF and Gündoğdu S: Does *Helicobacter pylori*-induced gastritis enhance food-stimulated insulin release? Dig Dis Sci 41: 1327-1331, 1996.
42. Calam J, Gibbons A, Healey ZV, Bliss P and Arebi N: How does *Helicobacter pylori* cause mucosal damage? Its effect on acid and gastrin physiology. Gastroenterology 113 (6 Suppl): S43-S49; discussion S50, 1997.
43. Verhulst PJ and Depoortere I: Ghrelin's second life: From appetite stimulator to glucose regulator. World J Gastroenterol 18: 3183-3195, 2012.
44. Isomoto H, Ueno H, Nishi Y, Wen CY, Nakazato M and Kohno S: Impact of *Helicobacter pylori* infection on ghrelin and various neuroendocrine hormones in plasma. World J Gastroenterol 11: 1644-1648, 2005.
45. Suzuki H, Masaoka T, Hosoda H, Ota T, Minegishi Y, Nomura S, Kangawa K and Ishii H: *Helicobacter pylori* infection modifies gastric and plasma ghrelin dynamics in Mongolian gerbils. Gut 53: 187-194, 2004.
46. Zhou X, Liu W, Gu M, Zhou H and Zhang G: *Helicobacter pylori* infection causes hepatic insulin resistance by the c-Jun/miR-203/SOCS3 signaling pathway. J Gastroenterol 50: 1027-1040, 2015.
47. Valenzuela MA, Canales J, Corvalán AH and Quest AF: *Helicobacter pylori*-induced inflammation and epigenetic changes during gastric carcinogenesis. World J Gastroenterol 21: 12742-12756, 2015.

48. Xi Y, Zhang XL, Luo QX, Gan HN, Liu YS, Shao SH and Mao XH: *Helicobacter pylori* regulates stomach diseases by activating cell pathways and DNA methylation of host cells. Front Cell Dev Biol 11: 1187638, 2023.
49. Ghafari F, Alizadeh AM, Agah S, Irani S and Mokhtare M: Insulin-like growth factor 1 serum levels in different stages of gastric cancer and their association with *Helicobacter pylori* status. Peptides 158: 170892, 2022.
50. Chichirau BE, Diechler S, Posselt G and Wessler S: Tyrosine kinases in *Helicobacter pylori* infections and gastric cancer. Toxins (Basel) 11: 591, 2019.
51. Choi JH, Cho SO and Kim H: α-Lipoic acid inhibits expression of IL-8 by suppressing activation of MAPK, Jak/Stat, and NF-κB in *H. pylori*-Infected gastric epithelial AGS cells. Yonsei Med J 57: 260-264, 2016.
52. Sokolova O, Vieth M, Gnad T, Bozko PM and Naumann M: *Helicobacter pylori* promotes eukaryotic protein translation by activating phosphatidylinositol 3 kinase/mTOR. Int J Biochem Cell Biol 55: 157-163, 2014.
53. Heckl SM, Wiesener V, Behrens HM, Ulase D, Krüger S and Röcken C: The expression of the insulin receptor in gastric cancer correlates with the HER2 status and may have putative therapeutic implications. Gastric Cancer 22: 1130-1142, 2019.
54. Yi HK, Hwang PH, Yang DH, Kang CW and Lee DY: Expression of the insulin-like growth factors (IGFs) and the IGF-binding proteins (IGFBPs) in human gastric cancer cells. Eur J Cancer 37: 2257-2263, 2001.
55. Guo C, Chu H, Gong Z, Zhang B, Li C, Chen J and Huang L: HOXB13 promotes gastric cancer cell migration and invasion via IGF-1R upregulation and subsequent activation of PI3K/AKT/mTOR signaling pathway. Life Sci 278: 119522, 2021.
56. Ge J, Chen Z, Huang J, Yuan W, Den Z and Chen Z: Silencing insulin-like growth factor-1 receptor expression inhibits gastric cancer cell proliferation and invasion. Mol Med Rep 11: 633-638, 2015.
57. Hidaka A, Sasazuki S, Goto A, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Noda M, Tajiri H, *et al*: Plasma insulin, C-peptide and blood glucose and the risk of gastric cancer: The Japan public health center-based prospective study. Int J Cancer 136: 1402-1410, 2015.
58. Xu L, Zhou R, Yuan L, Wang S, Li X, Ma H, Zhou M, Pan C, Zhang J, Huang N, *et al*: IGF1/IGF1R/STAT3 signaling-inducible IFITM2 promotes gastric cancer growth and metastasis. Cancer Lett 393: 76-85, 2017.
59. Zong CS, Chan J, Levy DE, Horvath C, Sadowski HB and Wang LH: Mechanism of STAT3 activation by insulin-like growth factor I receptor. J Biol Chem 275: 15099-15105, 2000.
60. Kanda N, Seno H, Konda Y, Marusawa H, Kanai M, Nakajima T, Kawashima T, Nanakin A, Sawabu T, Uenoyama Y, *et al*: STAT3 is constitutively activated and supports cell survival in association with survivin expression in gastric cancer cells. Oncogene 23: 4921-4929, 2004.
61. Judd LM, Bredin K, Kalantzis A, Jenkins BJ, Ernst M and Giraud AS: STAT3 activation regulates growth, inflammation, and vascularization in a mouse model of gastric tumorigenesis. Gastroenterology 131: 1073-1085, 2006.
62. Scalia P, Giordano A, Martini C and Williams SJ: Isoform- and paralog-switching in IR-Signaling: When diabetes opens the gates to cancer. Biomolecules 10: 1617, 2020.
63. Papachristoforou E, Lambadiari V, Maratou E and Makrilakis K: Association of glycemic indices (Hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. J Diabetes Res 2020: 7489795, 2020.
64. Zhou Y, Wang Y, Wang S and Shen L: Hyperglycemia promotes human gastric carcinoma progression via aquaporin 3. Dig Dis Sci 60: 2338-2345, 2015.
65. Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, Hu G and Sun Y: New horizons in tumor microenvironment biology: Challenges and opportunities. BMC Med 13: 45, 2015.
66. Liu J and Cao X: Glucose metabolism of TAMs in tumor chemoresistance and metastasis. Trends Cell Biol 33: 967-978, 2023.
67. Arner EN and Rathmell JC: Metabolic programming and immune suppression in the tumor microenvironment. Cancer Cell 41: 421-433, 2023.
68. Reinfeld BI, Madden MZ, Wolf MM, Chytil A, Bader JE, Patterson AR, Sugiura A, Cohen AS, Ali A, Do BT, *et al*: Cell-programmed nutrient partitioning in the tumour microenvironment. Nature 593: 282-288, 2021.
69. Wang JX, Choi SYC, Niu X, Kang N, Xue H, Killam J and Wang Y: Lactic acid and an acidic tumor microenvironment suppress anticancer immunity. Int J Mol Sci 21: 8363, 2020.
70. Liu Y, Li C, Lu Y, Liu C and Yang W: Tumor microenvironment-mediated immune tolerance in development and treatment of gastric cancer. Front Immunol 13: 1016817, 2022.
71. Shi J, Wu Z, Wu X, Huangfu L, Guo T, Cheng X, Han J, Li Z, Xing X and Ji J: Characterization of glycometabolism and tumor immune microenvironment for predicting clinical outcomes in gastric cancer. iScience 26: 106214, 2023.
72. Laplane L, Duluc D, Larmonier N, Pradeu T and Bikfalvi A: The multiple layers of the tumor environment. Trends Cancer 4: 802-809, 2018.
73. Boutilier AJ and Elsawa SF: Macrophage polarization states in the tumor microenvironment. Int J Mol Sci 22: 6995, 2021.
74. Ren J, Xu B, Ren J, Liu Z, Cai L, Zhang X, Wang W, Li S, Jin L and Ding L: The Importance of M1-and M2-polarized macrophages in glioma and as potential treatment targets. Brain Sci 13: 1269, 2023.
75. Gambardella V, Castillo J, Tarazona N, Gimeno-Valiente F, Martínez-Ciarpaglini C, Cabeza-Segura M, Roselló S, Roda D, Huerta M, Cervantes A and Fleitas T: The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target. Cancer Treat Rev 86: 102015, 2020.
76. Zhihua Y, Yulin T, Yibo W, Wei D, Yin C, Jiahao X, Runqiu J and Xuezhong X: Hypoxia decreases macrophage glycolysis and M1 percentage by targeting microRNA-30c and mTOR in human gastric cancer. Cancer Sci 110: 2368-2377, 2019.
77. Vitale I, Manic G, Coussens LM, Kroemer G and Galluzzi L: Macrophages and metabolism in the tumor microenvironment. Cell Metab 30: 36-50, 2019.
78. Cheng K, Cai N, Zhu J, Yang X, Liang H and Zhang W: Tumor-associated macrophages in liver cancer: From mechanisms to therapy. Cancer Commun (Lond) 42: 1112-1140, 2022.
79. Wang Y, Zhang J, Shi H, Wang M, Yu D, Fu M, Qian Y, Zhang X, Ji R, Wang S, *et al*: M2 Tumor-associated macrophages-derived exosomal MALAT1 promotes glycolysis and gastric cancer progression. Adv Sci (Weinh) 11: e2309298, 2024.
80. Wang ZH, Peng WB, Zhang P, Yang XP and Zhou Q: Lactate in the tumour microenvironment: From immune modulation to therapy. EBioMedicine 73: 103627, 2021.
81. Gao J, Liang Y and Wang L: Shaping polarization of tumor-associated macrophages in cancer immunotherapy. Front Immunol 13: 888713, 2022.
82. Tao L, Huang G, Song H, Chen Y and Chen L: Cancer associated fibroblasts: An essential role in the tumor microenvironment. Oncol Lett 14: 2611-2620, 2017.
83. Qiu Y, Lu G, Li N, Hu Y, Tan H and Jiang C: Exosome-mediated communication between gastric cancer cells and macrophages: Implications for tumor microenvironment. Front Immunol 15: 1327281, 2024.
84. Krzysiek-Maczka G, Targosz A, Wrobel T, Paw M, Szczyrk U, Opila J, Strzalka M, Wierdak M, Major P, Brzozowski T, *et al*: Time-extended exposure of gastric epithelial cells to secretome of *Helicobacter pylori*-activated fibroblasts induces reprogramming of gastric epithelium towards pre-cancerogenic and pro-invasive phenotype. Am J Cancer Res 12: 1337-1371, 2022.
85. Liu Y, Zhang X, Gu W, Su H, Wang X, Wang X, Zhang J, Xu M and Sheng W: Unlocking the crucial role of cancer-associated fibroblasts in tumor metastasis: Mechanisms and therapeutic prospects. J Adv Res 71: 399-413, 2025.
86. Jena BC, Das CK, Banerjee I, Bharadwaj D, Majumder R, Das S, Biswas A, Kundu M, Roy PK, Kundu CN and Mandal M: TGF-β1 induced autophagy in cancer associated fibroblasts during hypoxia contributes EMT and glycolysis via MCT4 upregulation. Exp Cell Res 417: 113195, 2022.
87. Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, Evans RM, Fearon D, Greten FR, Hingorani SR, Hunter T, *et al*: A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer 20: 174-186, 2020.
88. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL and Weinberg RA: Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 121: 335-348, 2005.
89. Pavlides S, Whitaker-Menezes D, Castello-Cros R, Flomenberg N, Witkiewicz AK, Frank PG, Casimiro MC, Wang C, Fortina P, Addya S, *et al*: The reverse Warburg effect: Aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. Cell Cycle 8: 3984-4001, 2009.
90. Chen L, Huang L, Gu Y, Cang W, Sun P and Xiang Y: Lactate-Lactylation hands between metabolic reprogramming and immunosuppression. Int J Mol Sci 23: 11943, 2022.

91. Xie J, Wu H, Dai C, Pan Q, Ding Z, Hu D, Ji B, Luo Y and Hu X: Beyond Warburg effect-dual metabolic nature of cancer cells. Sci Rep 4: 4927, 2014.
92. Dang CV: The interplay between MYC and HIF in the Warburg effect. Ernst Schering Found Symp Proc 4: 35-53, 2007.
93. Kim JW, Tchernyshyov I, Semenza GL and Dang CV: HIF-1-mediated expression of pyruvate dehydrogenase kinase: A metabolic switch required for cellular adaptation to hypoxia. Cell Metab 3: 177-185, 2006.
94. Xiao Y, Liu X, Xie K, Luo J, Zhang Y, Huang X, Luo J and Tan S: Mitochondrial dysfunction induced by HIF-1α under hypoxia contributes to the development of gastric mucosal lesions. Clin Transl Med 14: e1653, 2024.
95. Liao M, Yao D, Wu L, Luo C, Wang Z, Zhang J and Liu B: Targeting the Warburg effect: A revisited perspective from molecular mechanisms to traditional and innovative therapeutic strategies in cancer. Acta Pharm Sin B 14: 953-1008, 2024.
96. Liberti MV and Locasale JW: The warburg effect: How does it benefit cancer cells? Trends Biochem Sci 41: 211-218, 2016.
97. Kooshan Z, Cárdenas-Piedra L, Clements J and Batra J: Glycolysis, the sweet appetite of the tumor microenvironment. Cancer Lett 600: 217156, 2024.
98. Yoshida GJ: Metabolic reprogramming: The emerging concept and associated therapeutic strategies. J Exp Clin Cancer Res 34: 111, 2015.
99. Koppenol WH, Bounds PL and Dang CV: Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 11: 325-337, 2011.
100. Hayes C, Donohoe CL, Davern M and Donlon NE: The oncogenic and clinical implications of lactate induced immunosuppression in the tumour microenvironment. Cancer Lett 500: 75-86, 2021.
101. Liu Y, Zhang Z, Wang J, Chen C, Tang X, Zhu J and Liu J: Metabolic reprogramming results in abnormal glycolysis in gastric cancer: A review. Onco Targets Ther 12: 1195-1204, 2019.
102. Papandreou I, Cairns RA, Fontana L, Lim AL and Denko NC: HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab 3: 187-197, 2006.
103. Lu J, Tan M and Cai Q: The Warburg effect in tumor progression: Mitochondrial oxidative metabolism as an anti-metastasis mechanism. Cancer Lett 356 (2 Pt A): 156-164, 2015.
104. Yu Y, Jiang Y, Glandorff C and Sun M: Exploring the mystery of tumor metabolism: Warburg effect and mitochondrial metabolism fighting side by side. Cell Signal 120: 111239, 2024.
105. Liu T, Zhao X, Cai T, Li W and Zhang M: Metabolic reprogramming in *Helicobacter pylori* infection: From mechanisms to therapeutics. Front Cell Infect Microbiol 15: 1678044, 2025.
106. Ganapathy-Kanniappan S and Geschwind JF: Tumor glycolysis as a target for cancer therapy: Progress and prospects. Mol Cancer 12: 152, 2013.
107. Zhao Y, Liu H, Riker AI, Fodstad O, Ledoux SP, Wilson GL and Tan M: Emerging metabolic targets in cancer therapy. Front Biosci (Landmark Ed) 16: 1844-1860, 2011.
108. Ward PS and Thompson CB: Metabolic reprogramming: A cancer hallmark even warburg did not anticipate. Cancer Cell 21: 297-308, 2012.
109. Zhang D, Li J, Wang F, Hu J, Wang S and Sun Y: 2-Deoxy-D-glucose targeting of glucose metabolism in cancer cells as a potential therapy. Cancer Lett 355: 176-183, 2014.
110. Fontana F, Giannitti G, Marchesi S and Limonta P: The PI3K/Akt pathway and glucose metabolism: A dangerous liaison in cancer. Int J Biol Sci 20: 3113-3125, 2024.
111. Liu Q, Liu Z, Zhang X, Zeng A and Song L: Revisiting of cancer immunotherapy: Insight from the dialogue between glycolysis and PD-1/PD-L1 axis in the tumor microenvironment. Int J Biol Sci 21: 1202-1221, 2025.
112. Zhou Y, Chen S, Yang F, Zhang Y, Xiong L, Zhao J, Huang L, Chen P, Ren L, Li H, *et al*: Rabeprazole suppresses cell proliferation in gastric epithelial cells by targeting STAT3-mediated glycolysis. Biochem Pharmacol 188: 114525, 2021.
113. Fang Z, Zhang W, Wang H, Zhang C, Li J, Chen W, Xu X, Wang L, Ma M, Zhang S and Li Y: *Helicobacter pylori* promotes gastric cancer progression by activating the TGF-β/Smad2/EMT pathway through HKDC1. Cell Mol Life Sci 81: 453, 2024.
114. Wang TA, Xian SL, Guo XY, Zhang XD and Lu YF: Combined 18F-FDG PET/CT imaging and a gastric orthotopic xenograft model in nude mice are used to evaluate the efficacy of glycolysis-targeted therapy. Oncol Rep 39: 271-279, 2018.
115. Pu Z, Xu M, Yuan X, Xie H and Zhao J: Circular RNA circCUL3 accelerates the warburg effect progression of gastric cancer through regulating the STAT3/HK2 Axis. Mol Ther Nucleic Acids 22: 310-318, 2020.
116. Mueckler M and Thorens B: The SLC2 (GLUT) family of membrane transporters. Mol Aspects Med 34: 121-138, 2013.
117. Fenske W, Völker HU, Adam P, Hahner S, Johanssen S, Wortmann S, Schmidt M, Morcos M, Müller-Hermelink HK, Allolio B and Fassnacht M: Glucose transporter GLUT1 expression is an stage-independent predictor of clinical outcome in adrenocortical carcinoma. Endocr Relat Cancer 16: 919-928, 2009.
118. Modi N, Chen YH, Dong XC, Hu XM, Lau GW, Wilson KT, Peek RM Jr and Chen LF: BRD4 regulates glycolysis-dependent Nos2 expression in macrophages upon H pylori infection. Cell Mol Gastroenterol Hepatol 17: 292-308.e1, 2024.
119. Fujii T, Katoh M, Ootsubo M, Nguyen OTT, Iguchi M, Shimizu T, Tabuchi Y, Shimizu Y, Takeshima H and Sakai H: Cardiac glycosides stimulate endocytosis of GLUT1 via intracellular Na+,K+-ATPase α3-isoform in human cancer cells. J Cell Physiol 237: 2980-2991, 2022.
120. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, Kamada T, Irie T, Okumura G, Kono H, *et al*: Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell 40: 201-218. e9, 2022.
121. Zhou J, Wang W, Xie Y, Zhao Y, Chen X, Xu W, Wang Y and Guan Z: Proteomics-based identification and analysis of proteins associated with *Helicobacter pylori* in gastric cancer. PLoS One 11: e0146521, 2016.
122. Liu X, Yang Z, Chen Z, Chen R, Zhao D, Zhou Y and Qiao L: Effects of the suppression of lactate dehydrogenase A on the growth an d invasion of human gastric cancer cells. Oncol Rep 33: 157-162, 2015.
123. Zhao Z, Han F, Yang S, Wu J and Zhan W: Oxamate-mediated inhibition of lactate dehydrogenase induces protective autophagy in gastric cancer cells: Involvement of the Akt-mTOR signaling pathway. Cancer Lett 358: 17-26, 2015.
124. Fiume L, Vettraino M, Manerba M and Di Stefano G: Inhibition of lactic dehydrogenase as a way to increase the anti-proliferative effect of multi-targeted kinase inhibitors. Pharmacol Res 63: 328-334, 2011.
125. Fujiwara S, Kawano Y, Yuki H, Okuno Y, Nosaka K, Mitsuya H and Hata H: PDK1 inhibition is a novel therapeutic target in multiple myeloma. Br J Cancer 108: 170-178, 2013.
126. Deng X, Zhao J, Qu L, Duan Z, Fu R, Zhu C and Fan D: Ginsenoside Rh4 suppresses aerobic glycolysis and the expression of PD-L1 via targeting AKT in esophageal cancer. Biochem Pharmacol 178: 114038, 2020.
127. Jia L, Huang S, Yin X, Zan Y, Guo Y and Han L: Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction. Life Sci 208: 123-130, 2018.
128. Shiroki T, Yokoyama M, Tanuma N, Maejima R, Tamai K, Yamaguchi K, Oikawa T, Noguchi T, Miura K, Fujiya T, *et al*: Enhanced expression of the M2 isoform of pyruvate kinase is involved in gastric cancer development by regulating cancer-specific metabolism. Cancer Sci 108: 931-940, 2017.
129. Wang P, Sun C, Zhu T and Xu Y: Structural insight into mechanisms for dynamic regulation of PKM2. Protein Cell 6: 275-287, 2015.
130. Zhao X, Zhu Y, Hu J, Jiang L, Li L, Jia S and Zen K: Shikonin inhibits tumor growth in mice by suppressing pyruvate Kinase M2-mediated aerobic glycolysis. Sci Rep 8: 14517, 2018.
131. Lu J, Chen M, Gao S, Yuan J, Zhu Z and Zou X: LY294002 inhibits the Warburg effect in gastric cancer cells by downregulating pyruvate kinase M2. Oncol Lett 15: 4358-4364, 2018.
132. Chen S, Fisher RC, Signs S, Molina LA, Shenoy AK, Lopez MC, Baker HV, Koomen JM, Chen Y, Gittleman H, *et al*: Inhibition of PI3K/Akt/mTOR signaling in PI3KR2-overexpressing colon cancer stem cells reduces tumor growth due to apoptosis. Oncotarget 8: 50476-50488, 2016.
133. Shen Y, Chen M, Huang S and Zou X: Pantoprazole inhibits human gastric adenocarcinoma SGC-7901 cells by downregulating the expression of pyruvate kinase M2. Oncol Lett 11: 717-722, 2016.
134. Gao S, Song D, Liu Y, Yan H and Chen X: *Helicobacter pylori* CagA protein attenuates 5-Fu sensitivity of gastric cancer cells through upregulating cellular glucose metabolism. Onco Targets Ther 13: 6339-6349, 2020.

135. Hur H, Xuan Y, Kim YB, Lee G, Shim W, Yun J, Ham IH and Han SU: Expression of pyruvate dehydrogenase kinase-1 in gastric cancer as a potential therapeutic target. Int J Oncol 42: 44-54, 2013.
136. King CC and Obonyo M: *Helicobacter pylori* modulates host cell survival regulation through the serine-threonine kinase, 3-phosphoinositide dependent kinase 1 (PDK-1). BMC Microbiol 15: 222, 2015.
137. Tong J, Xie G, He J, Li J, Pan F and Liang H: Synergistic antitumor effect of dichloroacetate in combination with 5- fluorouracil in colorectal cancer. J Biomed Biotechnol 2011: 740564, 2011.
138. Xuan Y, Hur H, Ham IH, Yun J, Lee JY, Shim W, Kim YB, Lee G, Han SU and Cho YK: Dichloroacetate attenuates hypoxia-induced resistance to 5-fluorouracil in gastric cancer through the regulation of glucose metabolism. Exp Cell Res 321: 219-230, 2014.
139. Zhao M, Wei F, Sun G, Wen Y, Xiang J, Su F, Zhan L, Nian Q, Chen Y and Zeng J: Natural compounds targeting glycolysis as promising therapeutics for gastric cancer: A review. Front Pharmacol 13: 1004383, 2022.
140. Han S, Yang S, Cai Z, Pan D, Li Z, Huang Z, Zhang P, Zhu H, Lei L and Wang W: Anti-Warburg effect of rosmarinic acid via miR-155 in gastric cancer cells. Drug Des Devel Ther 9: 2695-2703, 2015.
141. Ai Y, Zhao Z, Wang H, Zhang X, Qin W, Guo Y, Zhao M, Tang J, Ma X and Zeng J: Pull the plug: Anti-angiogenesis potential of natural products in gastrointestinal cancer therapy. Phytother Res 36: 3371-3393, 2022.
142. Han JH, Kim M, Kim HJ, Jang SB, Bae SJ, Lee IK, Ryu D and Ha KT: Targeting lactate dehydrogenase a with catechin resensitizes SNU620/5FU gastric cancer cells to 5-fluorouracil. Int J Mol Sci 22: 5406, 2021.
143. Wang TA, Zhang XD, Guo XY, Xian SL and Lu YF: 3-Bromopyruvate and sodium citrate target glycolysis, suppress survivi n, and induce mitochondrial-mediated apoptosis in gastric cancer cells and inhibit gastric orthotopic transplantation tumor growth. Oncol Rep 35: 1287-1296, 2016.
144. Chen F, Zhuang M, Zhong C, Peng J, Wang X, Li J, Chen Z and Huang Y: Baicalein reverses hypoxia-induced 5-FU resistance in gastric cancer AGS cells through suppression of glycolysis and the PTEN/Akt/HIF-1α signaling pathway. Oncol Rep 33: 457-463, 2015.
145. Wu J, Zhang X, Wang Y, Sun Q, Chen M, Liu S and Zou X: Licochalcone A suppresses hexokinase 2-mediated tumor glycolysis in gastric cancer via downregulation of the Akt signaling pathway. Oncol Rep 39: 1181-1190, 2018.
146. Xu Y, Wang Q, Zhang L and Zheng M: 2-Deoxy-D-glucose enhances TRAIL-induced apoptosis in human gastric cancer cells through downregulating JNK-mediated cytoprotective autophagy. Cancer Chemother Pharmacol 81: 555-564, 2018.
147. Wang Y, Wang S, Yang Q, Li J, Yu F and Zhao E: Norepinephrine enhances aerobic glycolysis and may act as a predictive factor for immunotherapy in gastric cancer. J Immunol Res 2021: 5580672, 2021.
148. García-Carracedo D, Villaronga MÁ, Álvarez-Teijeiro S, Hermida-Prado F, Santamaría I, Allonca E, Suárez-Fernández L, Gonzalez MV, Balbín M, Astudillo A, *et al*: Impact of PI3K/AKT/mTOR pathway activation on the prognosis of patients with head and neck squamous cell carcinomas. Oncotarget 7: 29780-29793, 2016.
149. Sellam LS, Zappasodi R, Chettibi F, Djennaoui D, Yahi-Ait Mesbah N, Amir-Tidadini ZC, Touil-Boukoffa C, Ouahioune W, Merghoub T and Bourouba M: Silibinin down-regulates PD-L1 expression in nasopharyngeal carcinoma by interfering with tumor cell glycolytic metabolism. Arch Biochem Biophys 690: 108479, 2020.
150. Zhang B, Yang Y, Shi X, Liao W, Chen M, Cheng AS, Yan H, Fang C, Zhang S, Xu G, *et al*: Proton pump inhibitor pantoprazole abrogates adriamycin-resistant gastric cancer cell invasiveness via suppression of Akt/GSK-β/β-catenin signaling and epithelial-mesenchymal transition. Cancer Lett 356 (2, Part B): 704-712, 2015.
151. Stacpoole PW: Review of the pharmacologic and therapeutic effects of diisopropylammonium dichloroacetate (DIPA). J Clin Pharmacol J New Drugs 9: 282-291, 1969.
152. Raez LE, Papadopoulos K, Ricart AD, Chiorean EG, DiPaola RS, Stein MN, Rocha Lima CM, Schlesselman JJ, Tolba K, Langmuir VK, *et al*: A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 71: 523-530, 2013.
153. Maher JC, Krishan A and Lampidis TJ: Greater cell cycle inhibition and cytotoxicity induced by 2-deoxy-d-glucose in tumor cells treated under hypoxic vs aerobic conditions. Cancer Chemother Pharmacol 53: 116-122, 2004.
154. Novack DV: The FOX(O1) blasts off. Cell Metab 11: 175-176, 2010.
155. Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, Niven E, Maguire C, Gammer TL, Mackey JR, Fulton D, *et al*: Metabolic modulation of glioblastoma with dichloroacetate. Sci Transl Med 2: 31ra34, 2010.
156. Chu QS, Sangha R, Spratlin J, Vos LJ, Mackey JR, McEwan AJ, Venner P and Michelakis ED: A phase I open-labeled, single-arm, dose-escalation, study of dichloroacetate (DCA) in patients with advanced solid tumors. Invest New Drugs 33: 603-610, 2015.