Altered glycolysis results in drug-resistant in clinical tumor therapy (Review)

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Abstract. Cancer cells undergo metabolic reprogramming, including increased glucose metabolism, fatty acid synthesis and glutamine metabolic rates. These enhancements to three major metabolic pathways are closely associated with glycolysis, which is considered the central component of cancer cell metabolism. Increasing evidence suggests that dysfunctional glycolysis is commonly associated with drug resistance in cancer treatment, and aberrant glycolysis plays a significant role in drug-resistant cancer cells. Studies on the development of drugs targeting these abnormalities have led to improvements in the efficacy of tumor treatment. The present review discusses the changes in glycolysis targets that cause drug resistance in cancer cells, including hexokinase, pyruvate kinase, pyruvate dehydrogenase complex, glucose transporters, and lactate, as well the underlying molecular mechanisms and corresponding novel therapeutic strategies. In addition, the association between increased oxidative phosphorylation and drug resistance is introduced, which is caused by metabolic plasticity. Given that aberrant glycolysis has been identified as a common metabolic feature of drug-resistant tumor cells, targeting glycolysis may be a novel strategy to develop new drugs to benefit patients with drug-resistance.

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1. Introduction

Metabolic disorders, particularly those concerning glucose metabolism, play an important role in the proliferation and development of tumors (1). In normal cells, the energy provided for cell biological activity is predominantly dependent on changes in glucose metabolism that can transform glucose into pyruvate after several steps. Subsequently, pyruvate is converted to oxaloacetate, resulting in the production of citrate in the mitochondrial tricarboxylic acid cycle (TCA cycle). The process of glucose metabolism and the mitochondrial TCA cycle can generate energy in the form of adenosine triphosphate (ATP) and other forms, such as NADPH and FADH2 (1). NADPH and FADH2 are subsequently committed to the electron transport chain complexes to yield ATP, which is known as oxidative phosphorylation (OXPHOS) (2,3).

There are significant differences between normal cells and tumor cells regarding glucose metabolism. Warburg suggested that glycolysis is the predominant metabolic mechanism that produces the most ATP in cancer cells, which means that pyruvate derived from glucose is converted to lactate to exert its effects instead of being incorporated into the TCA cycle (2), and this is known as 'the Warburg effect'. Subsequently, the 'reverse Warburg effect' proposed that tumor-associated fibroblasts can produce large amounts of lactic acid via aerobic glycolysis, which is provided to

adjacent cells in a paracrine manner, causing the activation of mitochondria, increasing OXPHOS in adjacent cells and promoting tumor activity (3). Generally, 'the Warburg effect' and 'reverse Warburg effect' play an essential role in the development of cancer.

The incidence and mortality rates associated with cancer remain high, and despite the vast array of treatments available, chemotherapy resistance remains a significant challenge (4). There are several mechanisms of resistance, such as the mutation on binding sites, the activation of downstream effectors and the participation of alternative survival pathways to bypass target inhibition (5). In addition, cancer cells are resistant to immunotherapy via the Wnt-β-catenin signaling pathway, mitogen-activated protein kinase signaling pathways, cell cycle regulation signaling pathways and pathways activated based on the absence of the tumor suppressor phosphoinositide phosphatase, PTEN (6). Extensive research has been performed on glycolysis, which is considered a core process in tumor biological activity. Currently, increasing evidence suggests that that increased aerobic glycolysis is closely associated with chemotherapy resistance, even under O_2-rich conditions (7). For example, lapatinib and tamoxifen can induce resistance in breast cancer cells by promoting glycolysis (8-10). However, the clinical application of glycolysis inhibition through medical approaches is limited. Thus, it is essential to re-emphasize glycolysis in cancer cells to overcome therapy resistance. The present review summarizes some of the most common targets in drug-resistant tumor cells, investigates their role in the acquisition of drug resistance, and summarizes corresponding drugs against these targets to suppress chemotherapy resistance in tumor cells.

2. Glycolysis-related enzymes contribute to chemotherapy resistance in cancer cells

Increasing evidence suggests that glycolysis in cancer is associated with drug resistance (11,12). Aberrant expression of glycolysis-related enzymes, as regulators of glycolysis, induces glycolysis dysregulation, which contributes to tumorigenesis, tumor development and tumor therapy resistance (13).

Hexokinase (HK2). HK2 is a critical enzyme that promotes breast cancer progression and resistance via tumor glycolysis (14). HK2 blocks apoptosis by binding to the voltage-dependent anion channel (VDAC), which contributes to chemoresistance (15). Upregulation of HK2 expression can also induce chemotherapy resistance. Liu *et al* (14) demonstrated that by suppressing the mTOR-S6K signaling pathway, upregulation of HK2 promotes autophagy, subsequently conferring tamoxifen resistance to MCF-7 breast cancer cells.

In addition to upregulation of HK2 expression, its phosphorylation on Thr473 can also induce drug resistance. Proviral insertion in murine lymphomas 2 increases HK2 enzyme activity and enhances glycolysis by phosphorylating HK2 on Thr473, contributing to paclitaxel resistance (16). Conversely, SMI-4a can re-sensitize paclitaxel-resistant cells by dephosphorylating HK2 on Thr473 (17). In addition, an increase in HK2 dimers can also promote gemcitabine

resistance. Fan *et al* (18) reported that in pancreatic cancer, reactive oxygen species (ROS) derived from gemcitabine promote HK2 dimerization and bind to VDAC, which inhibits apoptosis by suppressing the formation of mitochondrial permeability transition pores, ultimately resulting in gemcitabine resistance (15,18).

Given the vital role of HK2 in tumor resistance, it can be used as a valuable target in investigating chemoresistance inhibition. HK2 inhibitor 3-bromopyruvate facilitates the dissociation of HK2 from the mitochondrial complex, potentiating daunorubicin-induced apoptosis and promoting leukemia cell sensitivity to daunorubicin (19) (Fig. 1). Furthermore, in ovarian cancer, the tyrosine analog, NK007, can overcome taxol resistance by degrading HK2 (20). In breast cancer, curcumin overcomes resistance to 4-hydroxytamoxifen by inhibiting snail family transcriptional repressor 2 (SLUG or SNAI 2) and subsequently downregulating HK2 expression (21). In a clinical study, the combination of docetaxel and curcumin for the treatment of patients with metastatic castration tolerant prostate cancer resulted in a high response rate, good tolerance and patient acceptability (22) (Table I). In another clinical study, lonidamine (LND), which inhibits aerobic glycolytic activity by influencing HK2 (23), was used with high dose epidoxorubicin for refractory epithelial ovarian cancer. The results indicated that this therapeutic strategy had an excellent second-line therapeutic activity for patients (23). Furthermore, the addition of LND to the carboplatin/cisplatin-paclitaxel standard regimen for advanced ovarian cancer was demonstrated to overcome cisplatin resistance in patients (24).

Phosphoglycerate mutase (PGAM1). PGAM1 facilitates the transformation of 3-phosphoglycerate to 2-phosphoglycerate in glycolysis. Its metabolic activity facilitates cancer metabolism and chemotherapy resistance (25). Previous studies have reported that PGAM1 is upregulated in different types of cancer, such as hepatocellular carcinoma (26), colorectal cancer (27,28) and lung cancer (29). The allosteric regulation of PGAM1 is an important mechanism to change the activity of PGAM1 (25). HKB99, a novel allosteric inhibitor of PGAM1, overcomes erlotinib resistance in non-small cell lung cancer (NSCLC) by enhancing oxidative stress and altering several signaling pathways, including JNK/c-jun activation, and AKT and ERK inhibition (25) (Fig. 1). However, Chen *et al* (30) discovered that the protein and mRNA expression levels of PGAM1 are downregulated in methotrexate-resistant cells. This phenomenon indicated that aberrant expression of PGAM1 may be associated with multidrug resistance (MDR) in breast cancer. Further studies are required to determine the molecular mechanism underlying drug resistance caused by PGAM1. In addition, few clinical studies have emphasized on exploiting the effect of PGAM1 inhibitors on tumor resistance.

Pyruvate kinase (PKM2). As a gatekeeper of pyruvate flux (1), PKM2 plays an important role in inducing chemotherapy resistance in different types of cancer. In prostate cancer, it has been demonstrated that PKM2 expression is upregulated in enzalutamide-resistant cells (31). Enhancer of zeste 2 polycomb repressive complex 2 subunit inhibitors or lysine
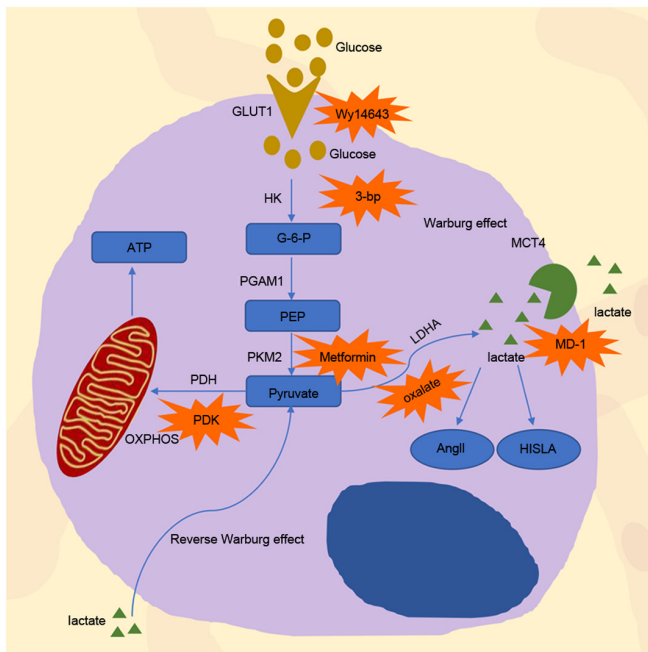
Figure 1. Process of glycolysis inside and outside the cell. G-6-P, glucose-6-phosphate; PEP, phosphoenol pyruvate; HK, hexokinase; PGAM, phosphoglycerate mutase; PKM2, pyruvate kinase; PDH, pyruvate dehydrogenase; LDH, lactate dehydrogenase; MCT4, monocarboxylate transporter 4; OXPHOS, oxidative phosphorylation; 3-bp, 3-bromopyruvate; PDK, pyruvate dehydrogenase kinase; MCT, monocarboxylic transporters; GLUT1, glucose transporters 1; AngII, angiotensin II; HISLA, HIF-1α-stabilizing long non-coding RNA.

demethylase 8 knockdown decrease PKM2 expression and result in prostate cancer cell sensitivity to enzalutamide (31). PKM2 also promotes chemotherapy resistance in ER⁺ breast cancer by enhancing aerobic glycolysis (32). In MCF-7 and T47D cells, upregulation of PKM2 hinders sensitivity to adriamycin amycin by enhancing glycolysis (32). Consistent with this result, 2-deoxy-D-glucose (2-DG), a PKM2 inhibitor, can inhibit glycolysis and restore the sensitivity to adriamycin amycin in MCF-7 and T47D cells (32). In addition, PKM2 is positively associated with chemotherapy resistance in pancreatic cancer (33), osteosarcoma (34), colorectal cancer (35) and gastric cancer (36).

PKM2 can translocate to the nucleus where it serves as a transcription coactivator, and this process can induce chemotherapy resistance (37). Ge *et al* (37) assessed PKM2 expression from nuclear and cytoplasmic extracts in breast cancer. The results demonstrated that PKM2 protein accumulated in the nucleus instead of the cytoplasm in response to overexpression of nicotinamide phosphoribosyl transferase, and induced resistance against tamoxifen in breast cancer cells. Furthermore, PKM2 translocation to the nucleus also leads to resistance to sorafenib and enzalutamide in liver and prostate cancers, respectively (31,34). Polypyrimidine tract-binding protein (PTBP1) is the primary regulator that affects PKM2 expression, and it can influence drug resistance in tumor cells by regulating PKM2 expression (35,38). In colon cancer, PTBP1 knockdown decreases PKM2 expression, inhibits glycolysis and increases cell sensitivity to vincristine and oxaliplatin (35). In addition, upregulation of PTBP1 expression in pancreatic ductal adenocarcinoma cells induces

PKM alternative splicing, which leads to resistance against gemcitabine (38).

It has been demonstrated that a series of drugs combined with chemotherapy drugs can increase the effectiveness of chemotherapy. Shikonin, an inhibitor of PKM2, combined with cisplatin exhibits a more significant cytotoxic effect by inducing necroptosis and ROS production compared with when either one is used alone (39). In osteosarcoma, treatment combined with metformin leads to the inhibition of glucose uptake, lactate production and ATP production by downregulating PKM2 expression. It can also diminish cisplatin resistance in osteosarcoma cancer stem cells (36,40) (Fig. 1). Metformin increases the antitumor effect of other chemotherapy drugs on osteosarcoma stem cells, such as adriamycin and 5-fluorouracil (36). Furthermore, high expression of the ATP binding cassette subfamily B member 1 (ABCB1) gene in patients with acute lymphoblastic leukemia (ALL) is associated with drug resistance and affects prognosis (41). In a clinical study, metformin combined with chemotherapy was particularly effective in patients with elevated ABCB1 expression (clinicaltrials.gov, NCT03118128) (41). In addition, ROS derived from NADPH oxidase 4 (NOX4) can suppress the P300/CBP-associated factor-dependent acetylation and lysosomal degradation of PKM2, leading to an increase in PKM2 expression and the occurrence of chemotherapy resistance (42).

Pyruvate dehydrogenase (PDH) complex. The PDH complex is composed of three enzymes that serve catalytic functions, named E1, E2 and E3. PDH is an E1 enzyme that can catalyze pyruvate conversion to acetyl coenzyme A in a rate-limiting reaction (43). Pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase mainly regulate PDH activity (43). PDK can inhibit PDH activity by phosphorylating PDH, whereas pyruvate dehydrogenase phosphatase can activate PDH by reversing the phosphorylation of this protein (43) (Fig. 1).

There are four subtypes of PDKs that participate in glycolysis and exert their effects on chemoresistance in tumor response, including PDK1-4 (43). In ovarian cancer cells, overexpression of PDK1 promotes cisplatin resistance (44). Overexpression of PDK1 increases epidermal growth factor receptor (EGFR) phosphorylation and promotes chemotherapy resistance in ovarian cancer (44). Through the transcriptional regulation of cyclin and CBS domain divalent metal cation transporter 3, PDK2 promotes lung adenocarcinoma cell proliferation and cisplatin resistance (45). Several studies have demonstrated that hypoxia-inducible factor (HIF)-1α regulates the expression of pyruvate dehydrogenase kinase 3 (PDK3) and further induces chemotherapy resistance under hypoxic conditions (43,46). Nucleus accumbens-1 mediates the inhibition of mitochondrial function via HIF-1α-mediated PDK3 overexpression, the inhibition of pyruvate dehydrogenase function and the repression of mitochondrial respiration (47). This process can protect cancer cells from apoptosis under hypoxic conditions (47). Upregulation of PDK4 increases resistance to chemotherapy in hepatocytes and colon cancer cells (48). In addition, PDK4 expression increases in tamoxifen-resistant MCF-7 cells, resulting in

augmented PDH activity and resistance to tamoxifen mediated by the phosphorylation of PDH (49).

Dichloroacetate (DCA) is a small molecule that promotes the entry of pyruvate into the mitochondria (50). By decreasing the expression of EGFR, DCA can sensitize MCF7 breast cancer cells to cell death induced by tamoxifen (51). The primary molecular mechanism underlying the antitumor effect of DCA involves the conversion of glycolysis into the oxidative metabolism of glucose, which decreases lactic acid production, promotes the production of cytotoxic reactive oxygen intermediates (52) and stimulates the Krebs cycle, and results in chemoresistance and radiotherapy resistance (53). Currently, several studies have combined DCA with some chemotherapy drugs and achieved remarkable results. For example, DCA plus cetuximab notably promotes tumor regression, whereas the use of either drug alone does not induce tumor regression (54). In addition, DCA combined with erlotinib or gefitinib significantly decreases EGFR activity and decreases resistance against tamoxifen (55). Other antitumor drugs have been developed based on the role of DCA. Mitaplatin, a synthetic drug based on cisplatin and DCA, not only destroys nuclear DNA through the action of cisplatin but also attacks mitochondria based on DCA in cancer cells. Under the influence of mitaplatin, the mitochondrial membrane gradient potential is altered in cancer cells, resulting in the release of cytochrome c, translocation of apoptosis-inducing factors from the mitochondria to the nucleus, and apoptosis (56). Due to these properties, mitaplatin can selectively kill tumor cells that are cultured with normal fibroblasts and partially overcome the resistance to cisplatin (56). 2,2-Dichloro-1-(4-isopropoxy-3-nitrophenyl) ethan-1-one(Cpd64) is a novel PDK1 inhibitor that is more efficient and specific than DCA and enhances the anticancer effect of EGFR-TKi (57). In a phase III clinical trial, devimistat (CPI-613), a PDH inhibitor, was combined with large doses of cytarabine and mitoxantrone to treat refractory acute myeloid leukemia and this combination achieved more favorable results (clinicaltrials.gov, NCT03504410) (58).

Lactate dehydrogenase (LDH). LDH controls the conversion and production of pyruvate and lactic acid (59). Previous studies have demonstrated that LDH is upregulated in several drug-resistant cells (60). Elevated LDH levels can mediate prostate cancer cell resistance to docetaxel (61), colorectal cancer cell resistance to cetuximab (62), oral cancer and breast cancer cell resistance to paclitaxel (60,63), and cartilage sarcoma cell resistance to doxorubicin (DOX) (64).

Several factors can change the expression of LDHA and therefore affect drug resistance. When cancer cells are in an anoxic environment, LDH plays a considerable part in anaerobic metabolism, which is inseparable from HIF-1α (65). It has been reported that LDH-5, an isozyme of LDH-1, can be induced by hypoxia, and the transcription of LDH-5 is directly regulated by HIF1 (65). Through the upregulation of LDHA, HIF-1α-overexpressing mutants (HIF-1α/ΔODD) are resistant to G_1 phase cell cycle arrest induced by cetuximab, and acquire cetuximab resistance in head and neck squamous cell carcinoma cell (66). ATP-binding cassette, subfamily C, member 3 (ABCC3), a member of the ATP-binding cassette (ABC) transporter family, is another factor that can alter LDHA levels (67). In human urinary bladder cancer (UBC)

cells that lack ABCC3, the blockade of LDHA signaling increases the sensitivity of UBC cells to cis-diamminedichloroplatinum (67).

Due to the critical role of LDHA in drug resistance, a combination of the LDHA inhibitor oxalate and paclitaxel can provide a synergistic inhibitory effect and clinical benefit against paclitaxel-resistant breast cancer due to the enhancement of apoptosis (60) (Fig. 1). Recently, galloflavin was identified as a novel LDH inhibitor that induces human breast cancer cell death by blocking different glycolytic pathways (68).

3. Glycolysis related substrates and products play roles in chemotherapy resistance

Glucose and glucose transporters (GLUTs). Changes in glucose can significantly affect the rate of glycolysis, leading to the occurrence of multiple drug resistance (69). Several studies have demonstrated that high glucose intake can induce cisplatin resistance in ovarian and bladder cancer cells, DOX resistance in breast cancer cells, and gemcitabine resistance in pancreatic cancer cells (18,70,71).

In terms of the molecular mechanism, when glucose is severely deficient, glucose regulated protein 78 (GRP78) expression is induced, leading to etoposide resistance and cisplatin susceptibility (71,72). GRP78 and B-cell lymphoma 2 (Bcl-2) competitively associate with Bcl-2 interacting killer (BIK), and upregulated GRP78 expression decreased the association between BIK and Bcl-2, subsequently inhibiting apoptosis and promoting drug resistance in breast cancer cells (73). Lee *et al* (72) performed a retrospective study and demonstrated a significant association between GRP78 and recurrence time in patients, suggesting that GRP78, which can predict chemotherapy outcomes, deserves further investigation. In a high glucose microenvironment, glucose promotes growth factor receptor signaling through the acetylation of acetyl-CoA-dependent Rictor, which activates rapamycin complex 2 to facilitate resistance to EGFR-, PI3K- or AKT-targeted therapy in glioblastoma (74). Furthermore, 2-DG combined with 5-fluorouracil can significantly improve its therapeutic effect in a high glucose microenvironment (75). 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) is a metabolic imaging tool used to detect lesions with increased glycolysis based on the glucose analog, fluorine-18 fluorodeoxyglucose (76). 18F-FDG PET can predict overall tumor behavior and sensitivity to treatment. In a clinical study, researchers successfully predicted the sensitivity to preoperative chemotherapy in patients with gastroesophageal cancer (77). Another clinical study demonstrated that 18F-FDG PET can predict treatment outcomes for 103/108 (95%) patients following two courses of conventional standard-dose chemotherapy for advanced Hodgkin's disease (78).

Glucose transports GLUTs primarily regulate glucose flux (79). Glucose transporters are mainly required for glucose uptake in cancer cells to promote cancer cell survival and resistance under hypoxic conditions. Currently, 14 GLUTs have been identified, which exhibit different substrate specificities and tissue expression patterns. Among these, GLUT1 is the most widely expressed transporter, and glucose

enters cells via glucose transporters to regulate the rate of glycolysis. Thus, GLUT1 dysfunction is associated with resistance (80). In different types of cancer, upregulation of GLUT1 is associated with poor prognosis (81). In NSCLC, activation of GLUT1-mediated glucose metabolism can cause cells to acquire gefitinib and erlotinib resistance (82). Furthermore, in colorectal cancer cells, overexpression of GLUT1 causes chemoresistance (83). In glioma cells, GLUT1 overexpression in paclitaxel-resistant cells restores glucose metabolism, resulting in paclitaxel resistance (84). In addition, in arginine deiminase-resistant cells, GLUT1 expression is increased, consistent with an increase in glycolytic pathway activation (85).

GLUT1 affects tumor cell resistance though several pathways. Activation of the yes-associated protein 1/TEA domain transcription factor 1 pathway may result in increased GLUT1 expression, thereby increasing cell viability in cisplatin-treated cancer cells, decreasing cell death and causing cisplatin resistance (86). The role of GLUT1 in chemotherapy resistance is associated with HIF-1α. Altered expression of GLUT-1 induced by HIF-1α is associated with augmented proliferation, chemotherapy resistance and metastasis (87). Genistein, a natural isoflavone, can re-sensitize aerobic glycolytic hepatocellular carcinoma cells to apoptosis by downregulating HIF-1α expression, inactivating GLUT1 and inhibiting aerobic glycolysis, resulting in decreased resistance to sorafenib (87).

Given the important role of GLUT1 in drug resistance, researchers have demonstrated several ways to overcome chemotherapy resistance by inhibiting this protein. In colorectal cancer cells, Wy14,643, a PPARα agonist, inhibits *GLUT1* transcriptional activity, decreases glucose uptake and blocks the mTOR pathway, which in turn decrease tumor growth and chemoresistance (88). GLUT1 can also react with other metabolites to potentiate anti-drug resistance. AG-PEG-SS-PLA, an aminoglucose (AG)-conjugated, redox-responsive nanomicelle from a single disulfide bond-bridged block polymer of polyethylene glycol and polylactic acid, can be formed by GLUT-1 and glutathione polymerization (89). Paclitaxel-loaded AG-PEG-SS-PLA nanomicelles activate the caspase-9 and caspase-3 cascade by upregulating pro-apoptotic proteins, such as Bcl2 associated X and BH3 interacting domain death agonist, and inhibiting Bcl-2, leading to apoptosis and improvement in MDR (89).

Lactate and acidic microenvironment. The Warburg effect implies that the main mechanism of glucose metabolism in cancer cells is aerobic glycolysis, whereas mitochondrial OXPHOS is inhibited, which enhances lactic acid production and consequently promotes the occurrence of drug resistance (60,90-92). Apicella *et al* (12) demonstrated that MET- or EGFR-addicted cancer cells exhibit increased glycolysis and lactic acid production following long-term utilization of tyrosine kinase inhibitors (TKIs). In cancer cells, lactic acid can promote the production of hepatocyte growth factor (HGF), in a nuclear factor kb-dependent manner. Overexpression of HGF upregulates MET expression by promoting signal transduction, which results in continuous resistance to TKIs. Decreased lactate production attenuates TKI resistance by inducing alterations to HGF and MET activity. In cervical cancer, chemotherapy resistance may be associated with the presence of L- and D-lactic acid in the cervix (93).

When the production of lactic acid increases, the acidic microenvironment changes. Cancer cells express several families of plasma membrane pH regulators to protect them and maintain normal physiological activities; these families are co-expressed and redundant on the plasma membrane, including carbonic anhydrase IX (CAIX), sodium-hydrogen antiporter 1 (NHE1) and the monocarboxylic transporters (MCT), particularly MCT1 and MCT4. These families can cause acidic by-products to be leaked from the cytoplasm, resulting in the dysregulation of pH in the tumor microenvironment, that is, alkalized intracellular fluid and acidified extracellular fluid (94). It has been reported that this form of metabolism can enhance resistance to radiation and chemotherapy (94-102).

The monocarboxylic transporters, MCT1 and MCT4, are mainly involved in the transport of lactic acid (Fig. 1). MCT1 is the most common monocarboxylic transporter expressed in p53-deficient tumors (103), whereas MCT4 expression is upregulated under hypoxic conditions and elevates with HIF induction (104). MCT1 is responsible for lactic acid uptake via oxidative cells, and MCT4 is responsible for the release of lactic acid from hypoxic cells (105). Abnormal expression of the MCT family is associated with drug resistance. Apicella *et al* (12) demonstrated that intratumoral lactic acid increases caused by high MCT1 expression are associated with poor prognosis. In addition, MCT1 is a major transporter that assists 3-bromopyruvate (3-BrPA) (106). Overexpression of MCT1 in cancer cells can sensitize tumor xenografts in response to 3-BrPA treatment *in vivo* (106). Conversely, downregulation of MCT4 can overcome anti-angiogenic therapy resistance (107). Based on the effects of MCT1 and MCT4, it is reasonable that the monocarboxylate transporter MCT1 and MCT4 dual inhibitor MD-1 can significantly inhibit oral squamous cell carcinoma, an invasive and therapeutic-resistant malignancy (108) (Fig. 1).

Carbonic anhydrase IX (CAIX or CA9) is a tumor-related metalloenzyme that can convert H_2O and CO_2 to HCO_3^- and H^+ ions reversibly, and is also induced by HIF (109). It has been reported that transient and long-term exposure to an extracellular acidic microenvironment (pH 6.7$\pm$0.1) increases CAIX expression in melanoma, breast cancer and colorectal cancer cells (109). Extracellular acidosis can cause chemotherapy resistance, which indicates that there may be an association between CAIX and chemotherapy resistance (110,111). Based on carbonic anhydrase CAIX staining in 188 microarray tumors, it was demonstrated that this protein is upregulated in basal cell-like breast tumors and is associated with chemotherapy resistance (110). Simultaneously, overexpression of CAIX in tongue cancer cells can promote chemotherapy resistance (111). SLC-0111, which inhibits CAIX, enhances the toxic effect of temozolomide and dacarbazine, and is currently being used for the treatment of advanced melanoma. SLC-0111 also increases the response of breast cancer cells to DOX and enhances the inhibitory effects of 5-fluorouracil on colon cancer (109).

NHE-1 is a plasma membrane glycoprotein composed of 815 amino acids, and it is a member of the elevated Na/H exchanger gene family, and is also known as a PH regulator.

Abnormal NHE-1 expression has been associated with drug resistance (112,113). For example, increased NHE1 expression can promote T cell-ALL resistance to DOX (113). In addition, cariporide, a NHE1 inhibitor, significantly increases breast cancer cell sensitivity to adriamycin by inducing apoptosis, promoting intracellular DOX accumulation and blocking the G_0/G_1 phase (114). Recently, cariporide, zoniporide and eniporide, which are effective and selective NHE-1 inhibitors, were demonstrated to be well tolerated in humans. However, only a few clinical trials have been performed in the field of oncology (115).

Due to the high rate of glycolysis, glucose levels within the tumor are deficient, and additional energy is in demand for normal physiological cancer cell activity (116); thus, other sources of energy are required. Excess pyruvate and lactate produced by glycolysis in cancer-associated fibroblasts can be delivered to adjacent cancer cells to enhance the mitochondrial activity, resulting in cancer cell resistance to many clinically used drugs, such as tamoxifen, used in endocrine therapy, Herceptin, used in Her-2-targeted therapy, and ebithromycin, used in chemotherapy (117). In breast cancer cells, this process can assist cancer cell survival in the presence of a lack of glucose for a long time, leading to PI3K/mTOR inhibitor resistance (116).

4. Glycolysis is associated with immunotherapy resistance

Recently, immunotherapy has been considered a milestone for cancer therapy. Programmed cell death 1 (PD1), PD1 ligand 1 (PD-L1), and checkpoint molecules, such as cytotoxic T lymphocyte antigen 4, have been identified, and drugs targeting them have been used on patients (118). Cancer immunotherapy has achieved significant breakthroughs and success. However, drug resistance has deterred clinical progression for several years. With a deeper understanding of immune mechanisms and immunotherapy efficacy, previous studies have acknowledged that tumors are resistant to immunotherapy via interferon (IFN) signaling and antigen presentation, the PI3K-AKT-mTOR axis, Wnt-β-catenin signaling, and deletion of the tumor suppressor phosphoinositide phosphatase, PTEN, which can activate different pathways (118-121).

Interferon binds IRF1 and the PD-L1 promoter via the Janus kinase 1 (JAK1)/JAK2-signal transducer and activators of transcription 1 (STAT1)/STAT2/STAT3-interferon regulatory factor 1 (IRF1) axis, thereby regulating the expression of PD-L1 and causing resistance to immune checkpoint inhibitors (119). The loss of copies of IFN-γ-mediated genes, such as *IFNGR1*, *IRF-1*, *JAK2* and *IFNGR2* can cause metastatic melanoma resistance to ipilimumab (anti-CTLA-4 therapy) (122). The loss of *JAK1* and *JAK2*, IFN-γ pathway genes, is associated with resistance to PD-1 therapy (122). Notably, the IFN signaling pathway can also alter glycolysis to cause chemotherapy resistance. Sustained STAT1 signaling causes chemotherapy resistance by increasing the expression of genes associated with glycolysis and OXPHOS (123) (Table II). STAT3 induces chemotherapy resistance by protecting mitochondrial oxidative phosphorylation and controlling the opening of mitochondrial permeability transition pores (124). In addition, IFN-γ signaling is downregulated in highly glycolytic tumor cells, and the disruption of tumor IFN-γ signaling
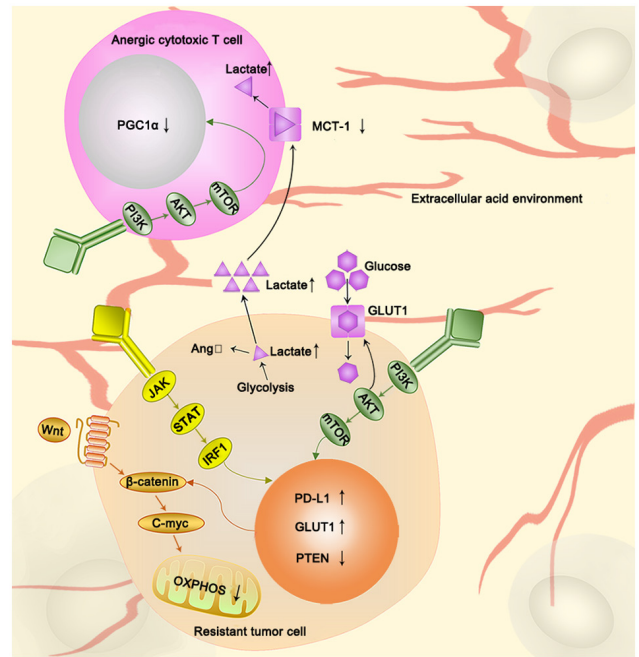

Figure 2. Glycolysis in tumor and tumor microenvironment is associated with immunotherapy resistance. STAT1 mediates tumor resistance to immunotherapy in the tumor microenvironment. Interferon regulates PD-L1 expression via the JAK1/JAK2-STAT1/STAT2-STAT3-IRF1 axis in tumor cells. STAT1 increases the expression of genes associated with glycolysis and oxidative phosphorylation. Wnt ligand inhibits mitochondrial function via the Wnt-β-catenin target gene, c-myc. However, PTEN loss can induce abnormal accumulation of β-catenin, and subsequently activate the Wnt-β-catenin signaling pathway. AKT also plays key roles in regulating immunotherapy resistance by decreasing PGC1α expression in tumor infiltrating lymphocytes and upregulating membrane localization of GLUT1. During the lactate producing process, PTEN-loss acts as an activator in tumor cells, and increased lactate induces an extracellular acid environment that inhibits MCT-1, which disturbs the metabolism in T-cells. STAT, signal transducer and activators of transcription; PD-L1, programmed cell death-ligand 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; GLUT, glucose and glucose transporters; MCT, monocarboxylic transporters; OXPHOS, oxidative phosphorylation; IRF1, interferon regulatory factor 1.

is an essential cause of tumor immunotherapy resistance (125). In clinical studies, the chimeric anti-CD20 antibody rituximab and IFN-alpha 2a combined immunotherapy has been proven effective (126,127). In another clinical study, the combination of interleukin-2 and α-IFN, based on a dose-increasing experiment, resulted in an increased response rate (128). These results indicate that the IFN signaling pathway is a good potential target for combination therapy (Fig. 2).

The metabolic reprogramming of tumor cells consumes a lot of energy and nutrients, which means that immune cells are in a state of nutrient depletion. The immune response to the tumor also has a significant negative effect (129). There is considerable evidence that the Wnt-β-catenin signaling pathway connects glycolysis to the immune response to the tumor. First, Wnt-β-catenin signaling is closely associated with glycolysis (130). The Wnt-β-catenin target gene, c-Myc, regulates and controls cancer cell metabolism (130). Wnt5B, a Wnt ligand, has been demonstrated to inhibit mitochondrial functions in triple negative breast cancer cells through c-Myc (131). Secondly, Wnt-β-catenin signaling is also associated with immunity. The Wnt ligand increases the expression

Table I. Overview of the clinical studies on the efficacy of glycolysis inhibitions in combination with chemotherapeutics.

Glycolysis inhibition	Chemotherapeutics	Glycolysis target	Cancer	(Refs.)
Metformin	Cisplatin	PKM2	Osteosarcoma	(36)
CPI-613	Cytarabine/Mitoxantrone	PDH	Acute myeloid leukemia	(58)
Lonidamine	Epidoxorubicin	HK2	Refractory epithelial ovarian cancer	(23)
	Cisplatin	HK2	Ovarian cancer	(24)
Curcumin	Docetaxel	HK2	Prostate cancer/Breast cancer	(22)

PKM2, pyruvate kinase; PDH, pyruvate dehydrogenase; HK, hexokinase.

of β-catenin in dendritic cells, and subsequently, the functions of Tregs and CD8+ T cells are activated, and antitumor immunity is suppressed (120). Thus, targeting the Wnt-β-catenin signaling pathway has become a strategy that can both target glycolysis and decrease immune resistance. Upon Wnt inhibition, the Wnt-β-catenin-target gene, *MCT1*, is also down-regulated, leading to a reduction in tumor microenvironment acidity, maintaining antitumor immunity, and preventing cell migration and metastasis (132). Accordingly, there is evidence that a combination of PD-1 and Wnt inhibitors can increase PD-1 inhibitor efficacy (133) (Fig. 2).

Overactivation of the pathological PI3K-AKT-mTOR pathway is the primary mechanism underlying immune checkpoint inhibitor resistance (134). AKT plays a vital role in the tumor microenvironment, whereby it decreases the expression of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) in tumor-infiltrating lymphocytes (TILs) within the tumor microenvironment. PGC1α can also regulate the biological function of mitochondria. Thus, a lack of this protein can cause TIL energy exhaustion and decrease antitumor immunity in the tumor microenvironment (135). Based on *in vitro* experiments, the addition of PGC1 inhibits tumor growth and increases overall survival (135) (Fig. 2).

AKT can promote glucose uptake by increasing the membrane localization of facilitative GLUT1 and GLUT4. AKT also contributes to the phosphorylation of HK-2 and stimulates its translocation to the mitochondria (135). All of these changes can affect glycolysis and induce chemotherapy resistance (135). Accordingly, PI3K-AKT inhibitors have become a focus of research because of their dual anti-chemotherapy and immunotherapy resistance effects (136). In phase I clinical studies, the AKT inhibitor afuresertib combined with carboplatin and paclitaxel exhibited promising results for the treatment of recurrent platinum-resistant ovarian cancer (137). However, clinical trials of AKT inhibitors for the immunotherapy-resistant disease remain to be performed (Fig. 2).

Glycolysis is also associated with immunotherapy resistance through PTEN-deficiency. The abnormal accumulation of β-catenin, caused by tumor-specific mutations, such as the specific loss of PTEN from melanocytes in lung cancer, leads to activation of the Wnt-β-catenin signaling pathway (138) (Fig. 2). PTEN-deficiency-associated and activated pathways can cause immune resistance. PTEN deficiency facilitates the immune escape of melanoma by restricting T cell access to tumor cells and preventing T cells from killing cancer cells (121). PI3Kβ

inhibitors can effectively reverse the immunotherapy resistance caused by the loss of PTEN (121). In PTEN-deficient melanoma cells, some substrates upregulation of glycolysis, such as pyruvate and lactate, provoke overactivation, which is characterized by adoptive T cell therapy resistance (125). A clinical study has demonstrated that in PTEN-deficient tumors, following treatment of metastatic castration-resistant prostate cancer with the Akt inhibitor ipatasertib coupled with the CYP17 inhibitor abiraterone, radiographic progression-free survival was extended compared with tumors without PTEN deficiency (139). This study further demonstrated that AKT inhibitors combined with antitumor drugs can play an important role in treating PTEN-deficient tumors.

Lactic acid levels are also associated with immune resistance. Lactic acid can be derived from tumor-associated glycolysis and from activated immune cells and macrophages (140). Lactate release in tumor cells also increases the expression of a myeloid-specific lncRNA, HIF-1α-stabilizing long non-coding RNA (HISLA) in macrophages, and elevated HISLA expression promotes aerobic glycolysis in tumor-associated macrophages through extracellular vesicles (EV) transport, which forms a pre-feedback loop (141) (Fig. 1). Blocking EV-mediated HISLA *in vivo* has been demonstrated to inhibit glycolysis and drug resistance in breast cancer (141). Furthermore, the excessive accumulation of lactic acid can cause immunosuppression, leading to resistance to immunotherapy. First, hypoxic tumor cells produce angiotensin II (AngII) through an anoxia-lactic acid-chymase-dependent mechanism (142). In the tumor microenvironment, local AngII is associated with cancer cell evasion of immune surveillance (143). In addition, the inhibition of AngII signaling may enhance tumor sensitivity to checkpoint immunotherapy (143) (Fig. 2). Secondly, lactic acid can impair the cytotoxic function of T cells. The activation of T cells uses glycolysis and relies on lactic acid secretion. The accumulation of intracellular lactic acid in the tumor cell causes an extracellular acidic environment, leading to the inhibition of MCT-1 (144). T cells cannot effectively secret lactate, and under these conditions, their metabolism is disordered, contributing to a significant reduction in cytotoxic activity, which severely affects T cell functionality (144) (Fig. 2). In addition, lactic acid can increase L-arginine-metabolizing enzyme arginase-1 (ARG1) expression in macrophages and inhibit the antitumor immune response (145). Following treatment with DCA, the declined *ARG1* mRNA expression can effectively reactivate the

Table II. Association between glycolysis and immune drug resistance.

Immunotherapy resistance target	Glycolysis target	Cancer	Correlation	(Refs.)
IFN/STAT1	ENO1	Squamous cell carcinoma	STAT1 increases the expression of ENO1	(123)
	LDHA	Squamous cell carcinoma	STAT1 increases the expression of LDHA	(123)
	PKM2	Squamous cell carcinoma	STAT1 increases the expression of PKM2	(123)
	OXPHOS	Mouse embryonal fibroblasts	STAT3 protects OXPHOS	(124)
Wnt-β-catenin	PDK1	Colon cancer cells	Blocking β-catenin decreases PDK1 level	(130)
	OXPHOS	TNBC	Knockdown of WNT5B attenuates mitochondrial biogenesis and OXPHOS	(131)
PI3K-AKT-mTOR pathway	GLUT1/4	Mouse embryonal fibroblasts	AKT increases the membrane localization of facilitative GLUT1 and GLUT4	(135)
	HK-2	Mouse embryonal fibroblasts	AKT contributes to the phosphorylation of HK-2 and stimulates its translocation to the mitochondria	(135)
PTEN-deficiency	Pyruvate/lactate	Melanoma	In PTEN-deficient melanoma cells, some glycolysis substrates are upregulated, such as pyruvate and lactate, which is characterized by adoptive T cell therapy resistance	(125)

IFN, interferon; STAT, signal transducer and activators of transcription; LDH, lactate dehydrogenase; PKM2, pyruvate kinase; OXPHOS, oxidative phosphorylation; GLUT1, glucose transporters 1; HK, hexokinase.

immune state regulated by lactic acid and improve antitumor immunotherapy benefits (145).

5. Transition of glycolysis to OXPHOS enhances drug resistance

The Warburg effect indicates that tumor cells tend to undergo glycolysis regardless of aerobic and anaerobic conditions, which implies that mitochondrial dysfunction is a feature of tumor cells (146). However, recently, this statement has been challenged (147). Several tumor cells have been reported to have metabolic plasticity, indicating a transformation from glycolysis to mitochondrial OXPHOS, leading to the production of vast amounts of energy and resistance to drugs (148). Recent evidence suggests that cancer cells can obtain glycolysis/OXPHOS mixed phenotypes, in which the ATP production is an outcome from both glycolysis and OXPHOS to support physiological activity of cells (149). In addition, cells with this characteristic are more likely to acquire drug resistance (150). When lactic acid increases, it can be used as an energy source by adjacent cancer cells to activate mitochondria and stimulate OXPHOS (151) (Fig. 1).

Such changes in OXPHOS can affect the drug resistance of tumor cells. Following chemotherapy, Farge *et al* (150) described a new method to identify and study acute myeloid leukemia (AML) cells remaining in the bone marrow. The results demonstrated that OXPHOS is increased in AML cells remaining in the bone marrow of mice following cytarabine therapy, and that the inhibition of OXPHOS can re-sensitize AML cells to cytarabine. In epithelial ovarian cancer, the oxygen consumption rate, mitochondrial respiration and oxidative phosphorylation in cisplatin-resistant cells were higher than those in cisplatin-sensitive cells (152). The activation of OXPHOS is a typical feature of hepatocellular carcinoma cell resistance to DOX (153). Generally, increased OXPHOS can promote the occurrence of chemotherapy resistance (150).

OXPHOS affects the treatment of tumors in several ways. As it results in the production of a large amount of ATP, this is bound to stimulate the activity of some transporters, one of which is drug transporters. In breast cancer cells, the continuous supply of ATP derived from OXPHOS is utilized by ABC transporters, leading to the outflow of DOX and the induction of an MDR phenotype (148). Tumor stem cells are also associated with drug resistance caused by OXPHOS. Increased OXPHOS mediated by mitochondria can stimulate tumor stem cells to expand, conferring resistance to tumor cells (154). Furthermore, NANOG, a stem cell marker, inhibits mitochondrial OXPHOS genes and promotes sorafenib resistance (155).

Several drugs inhibit the occurrence and development of tumors, and they can also affect OXPHOS. Some drugs, like cytarabine, 5-fluorouracil, TKIs, MAPKi and BRAFi can promote OXPHOS activity and increase drug resistance in the mitochondria, whereas others, such as anthracyclines, etoposide, sorafenib, paclitaxel and staurosporine, significantly decrease OXPHOS activity in the mitochondria (147). For those drugs that promote OXPHOS activity in mitochondria, it is necessary to find a better way to solve the associated drug resistance. Metformin is a type of mitochondrial inhibitor and combining it with cisplatin can attenuate cisplatin resistance in epithelial ovarian cancer cells (152). Metformin can also

be combined with TKIs to overcome tumor chemotherapy resistance (147). In addition, targeting mitochondrial respiration and HIF-1α may reverse tumor cell chemotherapeutic resistance (154). When the anoxic environment is destroyed and the HIF1α pathway is blocked, sex-determining region Y (SRY)-Box2 drives OXPHOS reprogramming, which helps tumor cells obtain an invasive oxidative tumor phenotype and enhance drug resistance and metastatic ability (156).

6. Conclusions

Changes in glycolysis, particularly increases in key enzymes and intermediates of this pathway, can affect the sensitivity of tumors to chemotherapeutic reagents, resulting in an increase in ATP production, and providing sufficient energy for the biological activity of tumor cells (14,69). This process enhances the repair of DNA damage, increases the phosphorylation, translocation into the nucleus, and autophagy-associated activity of enzymes, and causes drug resistance (157). In addition, several clinical trials have been performed to investigate the therapeutic effect of glycolysis-targeting therapy combined with clinical first-and second-line chemotherapeutic drugs on tumors (Table I).

Recently, several studies have demonstrated that the role of mitochondria in tumor metabolism is becoming essential. The reverse Warburg effect emerged, indicating that the increase in lactic acid as an energy material can be converted into pyruvate in the mitochondria and enhance mitochondrial activity and OXPHOS in adjacent cells (117). In addition, tumor cells also have metabolic plasticity. Glycolysis can be moderately transformed into OXPHOS when the external environment changes or there is plenty of oxygen around the tumor cells. This transformation is closely associated with chemotherapy (118,148). Increased mitochondrial activity and OXPHOS results in the production of higher levels of ATP and NADPH. High levels of ATP provide a vast amount of energy to tumor cells, and NADPH is a key antioxidant that can decrease ROS damage to tumor cells (158).

With an increase in studies on tumor immunity, immune checkpoint inhibitors have been developed for clinical applications (149). However, immunotherapy resistance is remains a major challenge. Based on a broadened understanding of tumor immunity, it is apparent that immunotherapy resistance is closely associated with glucose metabolism (125). The PI3K-AKT-mTOR axis, PTEN deficiency, IFN signaling and the Wnt-β-catenin signaling pathway can affect corresponding enzymes involved in glycolysis and enhance immunotherapy resistance (123,125,131,135). Conversely, the release of lactic acid, a glycolysis intermediate metabolite, can promote the occurrence of immunotherapy resistance. The interaction between glucose metabolism and immunotherapy resistance forms a positive feedback pathway and constitutes an important factor in tumor drug resistance (141). Currently, there are a few studies on the effect of the PI3K-AKT-mTOR axis, PTEN deficiency, IFN signaling, Wnt-β-catenin signaling pathway targeting agents on immunotherapy drug resistance, and chemotherapy resistance. The interdisciplinary study on tumor glycolysis and immunotherapy resistance should endeavor to receive more attention to proceed to understand the molecular mechanisms involved.

7. Future direction and perspectives

Regarding these glucose metabolic processes, targeted inhibitors may be used in combination with chemotherapy reagents or immune checkpoint inhibitors in the future. However, due to the lack of tumor drug resistance markers, targeted inhibitor prognostic indexes, and the specificity of these inhibitors, their clinical application is profoundly limited. In general, altered glycolysis, as a ubiquitous feature of drug-resistant tumor cells, represents a promising target, and novel strategy to overcome drug resistance clinically.

Availability of data and materials

Not applicable.

Authors' contributions

JP and YC designed the present review and drafted the initial manuscript. XW and YH analyzed the data. SX, WZ and SW revised the review for important intellectual content. ZF reviewed and critiqued the review following revisions. HX designed the present review, edited, reviewed and critiqued the manuscript. All authors have 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.

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