Acta Pharmaceutica Sinica B 2024;14(3):953−1008

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
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REVIEW

Targeting the Warburg effect: A revisited perspective from molecular mechanisms to traditional and innovative therapeutic strategies in cancer

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Received 5 July 2023; received in revised form 9 November 2023; accepted 14 November 2023

KEY WORDS

Warburg effect;
Cancer;
Regulatory factor;
LncRNAs;
miRNAs;
Traditional Chinese medicine;
Small-molecule drug;
Drug resistance

Abstract Cancer reprogramming is an important facilitator of cancer development and survival, with tumor cells exhibiting a preference for aerobic glycolysis beyond oxidative phosphorylation, even under sufficient oxygen supply condition. This metabolic alteration, known as the Warburg effect, serves as a significant indicator of malignant tumor transformation. The Warburg effect primarily impacts cancer occurrence by influencing the aerobic glycolysis pathway in cancer cells. Key enzymes involved in this process include glucose transporters (GLUTs), HKs, PFKs, LDHs, and PKM2. Moreover, the expression of transcriptional regulatory factors and proteins, such as FOXM1, p53, NF-κB, HIF1α, and c-Myc, can also influence cancer progression. Furthermore, lncRNAs, miRNAs, and circular RNAs play a vital role in directly regulating the Warburg effect. Additionally, gene mutations, tumor microenvironment remodeling, and immune system interactions are closely associated with the Warburg effect. Notably, the development of drugs targeting the Warburg effect has exhibited promising potential in tumor treatment. This comprehensive review presents novel directions and approaches for the early diagnosis

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Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2023.12.003

and treatment of cancer patients by conducting in-depth research and summarizing the bright prospects of targeting the Warburg effect in cancer.

1. Introduction

Cancer development is driven by abnormal signaling and metabolic reprogramming. Oncogenes closely relate to metabolic changes in cancer cells. Metabolic reprogramming is often mediated by various carcinogenic signals and controls cancer cell metabolism by altering the expression level and activity of key metabolic enzymes[1]. Therefore, a complete understanding of the relationship between oncoprotein and specific metabolism of cancer cells is conducive to developing of novel therapeutic strategies. In this manuscript, we begin with the current status of tumor glucose metabolism regulation therapy, address issues in current metabolic regulation research, and propose strategies for complex tumor glucose metabolism.

Glucose is the main energy source of life activity and tumor cell activity. In malignant tumor tissues, the glucose intake is much higher than that in normal tissues[2]. The metabolic imbalance resulting from restricting glucose absorption, specifically abnormal glycolytic gene expression, closely relates to tumor cell growth and developmen[3]. Under physiological oxygen concentration and functional mitochondria, tumor cells shift from oxidative phosphorylation to aerobic glycolysis, characterized by high glucose uptake and lactic acid production, known as the Warburg effect[4,5]. This metabolic pathway is crucial to cancer. It is also the reason that the growth rate of cancer cells is much faster than that of normal cells.

Warburg effect provides many benefits for cancer cells to compete and share energy. Even with sufficient oxygen supply, cancer cells increase energy supply through aerobic glycolysis due to improper proliferation and oncogenes' influence[6]. ATP is the main energy source of cell activity. Because of the hypoxia microenvironment and Warburg effect in tumors, tumor cells mainly undergo aerobic glycolysis, and 95% of ATP production is obtained through the glycoside-dependent mechanism[7]. Although compared with aerobic respiration, the amount of ATP generated during aerobic glycolysis under anaerobic conditions is very small, the expression of GLUT in tumor cells is often significantly increased. Its large amount of expression can meet the energy needs of tumor cells, accelerate the uptake of glucose by tumor cells, provide sufficient raw materials for aerobic glycolysis, and promote the production of ATP[8], which meets the needs of rapid tumor growth. Simultaneously, due to the substantial production of lactic acid, the cells reshape the tumor microenvironment, influencing the infiltration of various immune cells and closely correlating with tumor initiation, progression, invasion and metastasis.

Tumor cells at different stages of differentiation mainly rely on different modes of glucose metabolism. Cancer cells exhibit metabolic plasticity at different stages of metastasis. Changes in tumor metabolism can promote the occurrence of drug resistance. The Warburg effect also plays an important role in immune metabolism. LncRNAs, miRNAs, and Circular RNAs play a crucial role in regulating the glucose metabolism process of cancer. They mainly target and calibrate genes that regulate metabolism, causing changes in the metabolism of cancer cells, thereby affecting their growth, diffusion, and metastasis. This manuscript summarizes and analyzes the abnormal effects of glycolytic pathways in cancer, the mechanisms of key glycolytic enzymes and related signaling pathways, and the research progress of targeted drugs. It also explores the potential of combination therapy targeting complementary metabolic pathways to enhance or synergistically inhibit the survival of tumor cells. Metabolomics, an emerging technology, aims to study the abnormal metabolic patterns of tumors and holds promise for diagnosing and providing personalized treatment for tumor metabolic typing. It can also enable researchers to study the reprogramming of drug-resistant tumor cell metabolic networks more efficiently and systematically. At present, the mechanism of cancer occurrence and development is still unclear, especially since the research on its relationship with the Warburg effect is still in its infancy. Abnormal activity of aerobic glycolysis is a crucial feature of tumor cells, revealing its essential role in tumor occurrence and development, providing new ideas for early diagnosis and treatment of cancer, and developing new effective therapeutic targets is a challenging task.

2. Warburg effect: A glorious research history spanning a century

Glucose is an essential nutrient crucial for sustaining the life activities of animals. The energy of cells mainly comes from carbohydrate metabolism, which has two pathways, oxidative phosphorylation and aerobic glycolysis. According to the "Pasteur effect", low oxygen concentrations favor fermentation, while high oxygen levels inhibit it, promoting aerobic respiration and reducing aerobic glycolysis rates. This supports efficient energy utilization and carbon use for synthesis reactions. Since NADH can enter mitochondria and undergo oxidation, it inhibits lactic acid production. During hypoxia, NADH cannot be oxidized through the respiratory chain, and pyruvate acts as a hydrogen acceptor to reduce to lactate[9]. Therefore, normal cells are inhibited from aerobic glycolysis under aerobic conditions, mainly utilizing aerobic respiration. In 1923, German biochemist Otto Heinrich Warburg discovered significant differences in the carbohydrate metabolism of tumor cells compared to normal cells[5]. During the process of malignant proliferation, the energy metabolism pathway was reshaped, and the energy metabolism pathway of cancerous cells changed from the tricarboxylic acid cycle to aerobic glycolysis. Otto Warburg noted that even with sufficient oxygen, tumor cells favor aerobic glycolysis over oxidative phosphorylation for energy production due to its efficiency[5]. This phenomenon was subsequently coined the term "Warburg effect" by E. Racker in 1976[10]. Warburg effect is

considered to be the metabolic reconstruction of tumor cells in order to adapt to the energy needs of proliferation and differentiation. This effect provides a number of ATP for the growth and proliferation of tumor cells, creates a microenvironment fitable for tumor cells to survive, and enhances invasion and metastasis ability, and also helps tumor cells escape from the mechanism of body immunity and cell apoptosis[11]. Otto Warburg was honored with the Nobel Prize in Physiology or Medicine in 1931 for discovering cellular respiratory oxidotransferase. In 1956, Otto Heineieh Warburg further demonstrated that the Warburg effect originated from "irreversible respiratory system damage" caused by mitochondrial dysfunction. However, during the 20 years from 1952 to 1976, a large number of researchers successively demonstrated that most tumors were not accompanied by mitochondrial dysfunction while aerobic glycolysis was upregulated, opposing Warburg's initial "respiratory injury theory". However, there are still misunderstandings about the reasons for the Warburg effect and its relationship with mitochondrial oxidative metabolism. From 1964 to 1965, researchers separated type I, II, III and IV hexokinase (HK) isoenzymes by ion exchange chromatography and electrophoresis[12,13]. In 1965, it was discovered that the absence of phosphofructose can lead to glycogen storage disease type VII[14]. In 1969, Louis Sokoloff employed the glucose analogue 2-deoxy-D-glucose (2-DG), which can readily penetrate the blood−brain barrier (BBB), in positron emission tomography (PET) imaging to assess glucose utilization in the brain[15]. Moreover, Louis Sokoloff synthesized the most widely used radioactive tracer 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-DG or FDG) in 1996[16]. Glucose transporter type 1 (GLUT1), a protein that transports glucose, was first isolated from red blood cells in 1977[17]. The *GLUT1* gene sequence was identified in 1985[18]. In the same year, researchers pointed out the importance of HK2's synthesis and metabolism through the pentose phosphate pathway[19]. In 1994, it was discovered that HK2 was highly expressed in tumors. However, due to the already discovered abnormal glucose metabolism in tumors, researchers were still unable to confirm whether the function of HK2 in tumors was similar to that in normal tissues[20]. Subsequently, researchers developed an interest in studying HK2 as a potential target in tumors. As one of the metabolic characteristics in tumor cells, Warburg effect has been found for a hundred years. It has been widely studied and deeply discussed in recent 20 years. At present, there are many explanations for the universal Warburg effect in tumor cells. Since 1998, researchers have successively confirmed that cancer cells heavily depend on mitochondrial respiration, and mitochondrial dysfunction can contribute to the development of the Warburg effect[21−24]. In 2000, researchers began using 2-DG to evaluate *in vitro* and *in vivo* glucose uptake activity without the use of radioactive substances[25]. Subsequently, it was proven that 2-DG as a glucose metabolism inhibitor mainly inhibits aerobic glycolysis by acting on HK2[26]. In 2004, researchers confirmed that the Warburg effect is not a simple adaptation to hypoxia[27]. In 2009, Lewis C. Cantley and Craig B. Thompson reviewed the "Warburg effect" in the journal *Science*, revealing that some signal transduction pathways associated with cell proliferation can also control metabolic pathways responsible for synthesizing nutrients into biomass[28]. Some cancer-related mutations enable tumor cells to obtain and metabolize nutrients in a way conducive to proliferation rather than efficiently producing ATP. It is suggested that a further understanding of the relationship between cell metabolism and growth control may ultimately be beneficial to the treatment of cancer. In 2011, the Warburg effect is considered a core feature of the malignant phenotype of cancer and is referred to as a "marker of cancer"[29]. In the same year, PKM2 inhibitor Shikonin was discovered to hold potential for treating tumors by inhibiting the Warburg effect through impeding the final rate-limiting step of aerobic glycolysis[30]. In 2012, researcher Yi et al.[31] revealed in the journal *Science* that O-linked *β*-*N*-acetylglucosamine (*O*-GlcNAc) induces glycosylation at Ser529 of phosphofructokinase-1 (PFK1) in response to the hypoxic state of cancer cells, inhibits PFK1 activity, and then redirects glucose flux during aerobic glycolysis to the PPP, providing the energy required for cancer cell growth through compensation. Inhibiting glycosylation at PFK1 Ser529 can inhibit cancer cell proliferation and tumor tissue growth. The regulatory mechanism of PFK1 in aerobic glycolysis in cancer has been revealed, suggesting that inhibiting PFK1 glycosylation may provide a new therapeutic approach for combating cancer. In 2014, Professor Yan Ning's research group in Tsinghua University School of Medicine analyzed the crystal structure of human glucose transporter GLUT1 for the first time in the journal *Nature*, revealing the process of the transport of essential substances in the human body to the cell membrane, which brings therapeutic prospects for manual intervention as a potential target of disease diagnosis or drug development[32]. In 2015, Bradley A. Webb's team first analyzed the biological crystal structure of mammalian PFK1 tetramers in the journal Nature, which helps people understand the functional changes caused by PFK1 mutations in diseases, and based on this, developed anti-tumor drugs targeting PFK1 to affect the warburg effect[33]. In 2020, Professor Olivier Pourqui é's team from Harvard Medical School published an interesting research online in the journal *Nature*[34]. The research found the close similarity between the developing tail bud cells and the cancer cells (high pHi and low pHe) showing high Warburg metabolism, suggesting that some tumor cells will reactivate the developmental metabolic program. In 2021, Ming's team of Memorial Sloan Kettering Cancer Center in the United States published a study in the journal *Science* that offered a fresh perspective on the "Warburg effect"[35]. This study shows that there is an undiscovered link between Warburg metabolism and the activity of phosphatidylinositol three kinase (PI3K), which is realized by latate dehydrogenase A (LDHA). Tumors cells can use Warburg metabolism to maintain the biological activity of PI3K signaling pathway, thus ensuring the continuous proliferation of cancer cells. This discovery challenges the view in textbooks for a long time. More importantly, this study proposes a promising cancer treatment method. By inhibiting the Warburg "switch" of LDHA, it can inhibit the growth of cancer cells and then be used to treat cancer (Fig. 1A).

A prominent metabolic alteration in tumor cells is the persistent abnormal activation of aerobic glycolysis, even under aerobic conditions, known as the Warburg effect, also names aerobic glycolysis. The classic Warburg effect in tumor cells consists of several precise steps in succession: firstly, glucose is transported to tumor cells at high speed *via* GLUTs and sodium−glucose junction transporter 1, and then phosphorylated into glucose-6 phosphate by HK, which is a speed-limiting step that provides direct feedback inhibition to preserve energy. HK combines with mitochondrial membrane and has high affinity for glucose, which is helpful to start aerobic glycolysis at low glucose level. Next, glucose-6-phosphate isomerase (GPI)

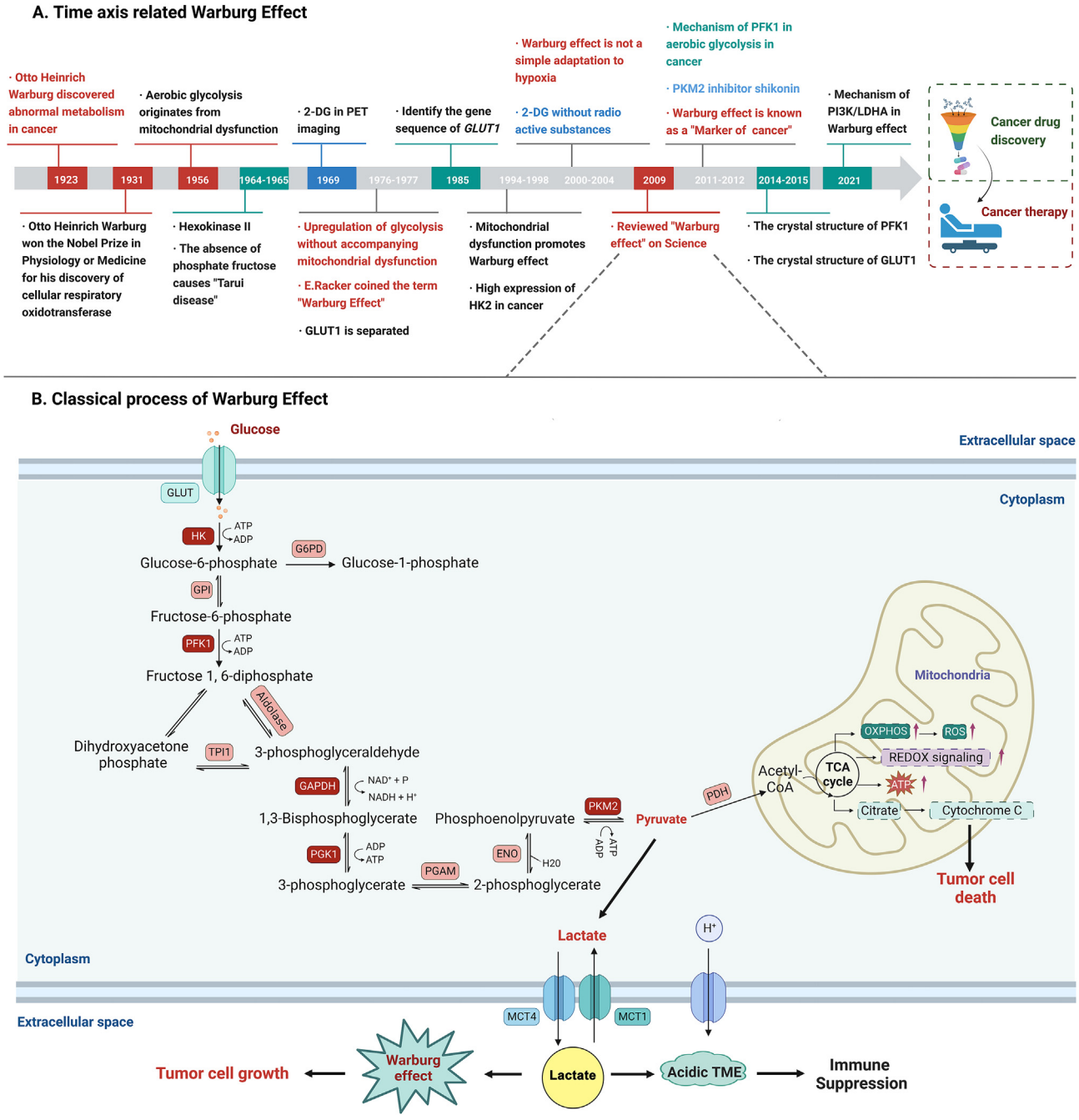


Figure 1 The timeline and classic process of the Warburg effect. (A) The timeline of the Warburg effect from target discovery to drug development. (B) The classic process of the Warburg effect from glucose to lactate. The pyruvate produced by aerobic glycolysis also enters the tricarboxylic acid cycle inhibiting the Warburg effect.

converts glucose-6-phosphate into fructose-6-phosphate. Fructose-6-phosphate is then phosphorylated to produce fructose-1,6-diphosphate and fructose 2,6-diphosphate, facilitated by PFK1 and PFK2, with the consumption of an ATP molecule. Secondly, aldolase converts fructose-1,6-diphosphate into glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. Glyceraldehyde-3-phosphate is converted from glyceraldehyde-3-phosphate dehydrogenase to glycerate 1,3-diphosphate, and then converted from phosphoglycerate kinase to glycerate 3-phosphate to generate two ATP molecules. Phosphoglycerate mutase isomerizes 3-phosphoglycerate to 2-phosphoglycerate, and then forms phosphoenolpyruvate. Finally, PEP is converted into pyruvate to generate an ATP molecule through the rate limiting step of aerobic glycolysis catalyzed by pyruvate kinase (Fig. 1B).

3. Warburg effect in cancer

Aerobic glycolysis is an adaptive metabolic change in tumor tissue, leading to cancer being considered a metabolic disease.

Besides facilitating the rapid production of ATP in tumor tissues, aerobic glycolysis provides tumor cells with essential metabolic intermediates and precursors for phospholipid and nucleic acid synthesis. It also shields cancer cells from chemotherapy drug damage[36]. The Warburg effect, characterized by low efficiency but rapid metabolism, consumes substantial glucose in the tumor microenvironment. It synthesizes necessary precursor substances for rapid tumor proliferation and secretes lactic acid, creating an immunosuppressive microenvironment conducive to tumor growth and metastasis[37]. Warburg effect can promote the upregulation of the expression of HK, GLUT, LDH, PK and 3-phosphoinositide-dependent protein kinase 1 (PDK1), improve the tolerance of tumor cells to hypoxia conditions, and then promote the invasion and metastasis of malignant tumors. Therefore, the metabolic mode targeting tumor cells is theoretically a strategy to fundamentally solve the malignant transformation of tumors. Now, after many years of clinical research on anti-tumor strategies for oncogenes fell into difficulties, the metabolic mode of tumor cells has attracted people's attention again. Anti-cancer drugs based on Warburg effect have gradually become a hot spot in tumor research.

Different initial lesions of tumors depend on different metabolic pathways. Ovarian cancer stem cells overexpress genes concerned with glucose uptake, oxidative phosphorylation (OXPHOS) and fat acid oxidation (FAO), and also overexpress the key enzyme for pyruvate to enter TCA cycle, preferring pyruvate to enter TCA, maintaining OXPHOS metabolic characteristics[38]. In high-grade glioma tissue, glioma stem cells mainly gather in two specific regions, around tumor blood vessels and necrotic areas with poor blood supply. The characteristics of the two microenvironments are completely different, with the former having relatively abundant oxygen content and sugars, while the latter has the opposite. However, as the tumor progresses, the proportion of the latter will gradually increase. On the other hand, based on differences in genetic phenotypes, glioma stem cells can be divided into at least two subtypes, namely the pre neuronal type and the mesenchymal type[39]. The biological characteristics of glioma stem cells are intricately linked to their microenvironment. Research has found that glioma stem cells clustered in hypoxic necrotic areas are mainly mesenchymal cells with relatively high malignancy, and the hypoxic microenvironment is conducive to maintaining stem cell characteristics such as self-replication and low differentiation. Conversely, glioma stem cells in the surrounding area of tumor blood vessels are mainly neuronal type with lower malignancy. It is worth noting that with the dynamic process of tumor volume growth and angiogenesis, changes in the microenvironment will promote the epithelial mesenchymal transition of glioma stem cells by affecting the glucose metabolism mode of stem cells and the expression of other regulatory factors[40]. Similar to other tumor cells, glioma stem cells highly depend on aerobic glycolysis to maintain their own energy supply even under relatively normal oxygen levels. Research results from the Anderson Cancer Center in the United States further validate this theory[41]. The aerobic glycolysis level of brain glioma stem cells, especially mesenchymal glioma stem cells, significantly increased, becoming the primary mode of energy metabolism[41]. However, compared with ordinary high-grade glioma cells, the glucose uptake level of glioma stem cells is relatively low, and the ATP production is higher than that of high-grade glioma cells, indicating that OXPHOS is still an important energy source of glioma stem cells[42]. This may be attributed to the heterogeneity of glucose metabolism in glioma stem cells from varying tissue sources or genotypes. OXPHOS and aerobic glycolysis mutually complement each other in glioma stem cells, and the glucose metabolism mode of these cells exhibits heterogeneity across different growth and development stages. Tumor cells at different differentiation stages mainly depend on different glucose metabolism modes[43], the level of aerobic glycolysis is also regulated differently.

3.1. *Cancer initiation and progression*

Over-proliferation is one of the most important malignant behaviors of tumor cells. Most of the energy that tumor cells need to absorb in the process of proliferation mainly comes from the aerobic glycolysis of Warburg effect. Warburg effect plays an essential role in tumorigenesis and development[44]. Cells have different metabolic characteristics at different stages. Based on the different metabolic characteristics at various stages of the disease, the researchers put forward the hypothesis that the continuous activation of genes promotes the metabolic changes in the process of tumor development[45]. The first wave of oncogene activation transformed tumor cell metabolism into partial glycolytic phenotype. At this time, the imbalance of tumor cell proliferation and angiogenesis leads to hypoxia of tumor cells, triggering the activation of the second wave of genes, accelerating aerobic glycolysis, leading to the classic "Warburg" phenotype and almost completely inhibited OXPHOS. The imbalance between high energy demand and nutrient shortage of tumor cells induced the third wave of gene expression, and tumor cells supported their survival through glutamine. α-Ketoglutaric acid from glutamine enters TCA, re-establishes OXPHOS, and provides ATP and NADPH. Retrograde signals from these reactivated mitochondria trigger the fourth wave of gene recoding to regulate mitochondrial biogenesis and degradation[45]. The activation of different oncogenes under different metabolic states further induces the plasticity of tumor metabolism so that tumor cells can make the best use of available metabolic substrates and adapt to the rapidly changing microenvironment. As ovarian cancer progresses, glucose and fatty acid oxidation decrease significantly, leading to increased lactic acid production and a shift towards glycolytic metabolism[46]. In addition, compared with benign or advanced ovarian cancer cells, the initial cells of ovarian cancer have reduced oxidation of glucose and fatty acids, increased aerobic glycolysis, and tended to aerobic glycolysis phenotype[47]. Unlike most cells, normal prostate epithelial cells are highly dependent on glycolytic metabolic capacity. In the early stage of prostate cancer, cells gradually changed to OXPHOS-dependent metabolic mode, and in the tumor progression stage, cells preferentially carried out aerobic glycolysis metabolism. Therefore, prostate cancer cells use aerobic glycolysis and OXPHOS to supply energy at different stages of disease progression[48]. It is worth noting that there are also differences in metabolic characteristics between breast cancer and normal breast tissue, which reflects the heterogeneity and complexity of breast cancer[49]. Apart from glucose, amino acids like glutamine and serine serve as crucial substrates for cell growth and proliferation. When tumor cells take up glutamine, it undergoes conversion to glutamate through the action of glutaminase (GLS). Differential expression of GLS has been observed in breast cancer tissue, depending on the breast cancer subtype[50].

Reprogramming of energy metabolism is considered a hallmark that promotes tumor onset and progression[51]. Oncogenes drive the imbalance of metabolic pathways, which provides selective advantages for tumor cells, enabling them to proliferate highly in harsh microenvironments and improving their survival rate[52]. In addition, metabolites produced by energy metabolism

Reprogramming interact with signal transduction pathways to promote the occurrence of tumors. Changes in the metabolic program of tumor cells also further affect other cells in the tumor microenvironment, helping to regulate processes closely related to tumor development[53]. The metabolic effects of tumors reveal key factors in the occurrence and development of tumors, opening up new diagnostic and therapeutic perspectives (Fig. 2A).

3.2. Cancer metastasis

The primary cause of tumor resistance, metastasis and recurrence is the presence of a small number of tumor cells with strong stem cell characteristics, including self-renewal ability and multiple differentiation capability, known as "cancer stem cells (CSCs)"[54]. Due to the presence of CSCs, tumor cell lines can exhibit certain stemness. The strength of tumor cell lines can reflect their malignancy and potential for malignant events such as metastasis and drug resistance[55]. The metabolic transformation from oxidative phosphorylation to aerobic glycolysis can affect tumor cell stemness and participate in regulating tumor invasion and distant metastasis. Pancreatic cancer cells showed extensive enhancement of aerobic glycolysis, including overexpression of glycolytic enzymes and increased production of lactic acid, which regulated tumor cell metastasis by promoting epithelial−mesenchymal transformation, tumor angiogenesis and metastasis and colonization of distant organs[56]. The tumor cells in the process of metastasis isolated from the blood, compared with the tumor cells in the primary tumor or lung metastasis, have the priority of OXPHOS[57]. Compared with solid tumor cells, tumor cells isolated from ascites of ovarian cancer patients tend to express glycolytic phenotype, suggesting that the glycolytic rate decreases after tumor attachment and growth[47]. It further supports the concept of metabolic plasticity of cancer cells at different stages of metastasis. In addition, the researchers found that once the tumor cells leave the primary focus, they will have metabolic changes different from the primary focus to facilitate survival after metastasis. The metastatic tumor cells exhibit distinct metabolic advantages depending on the metastatic organ. Breast cancer cells isolated from bone or lung metastases prioritize OXPHOS, whereas breast cancer cells from liver metastases primarily exhibit aerobic glycolysis.

Although aerobic glycolysis is a known feature of tumor cells, the metabolic transformation from oxidative phosphorylation to aerobic glycolysis may regulate tumor invasion and distal metastasis by promoting epithelial−mesenchymal transition, tumor angiogenesis and epigenetic modification, but targeting this metabolic pathway has not yet been successfully translated into clinical practice. The significant metabolic heterogeneity and cellular plasticity observed in solid tumors make it unlikely that metabolic inhibitors will be effective as a single therapy for cancer, but combination therapy with two or more drugs that simultaneously inhibit different metabolic pathways can be considered to reduce drug toxicity and prevent recurrence. In addition, aerobic glycolysis-related inhibitors may contribute to the sensitization of tumor cells and improve the treatment outcomes of drug-resistant relapse, providing new treatment or prevention strategies for combating cancer (Fig. 2B).

3.3. Cancer immune microenvironment

The tumor microenvironment consists of tumor-infiltrating monocytes/macrophages, immunosuppressive cells, fibroblasts, vascular system and inflammatory factors secreted by them. Tumor metabolism and tumor immune microenvironment interact with each other. The metabolism of tumor is mainly aerobic glycolysis. The accumulation of lactic acid produced by aerobic glycolysis will cause the tumor immune microenvironment to be in an acidic state. At the same time, the growth of tumor cells requires a lot of energy, which can also cause the tumor immune microenvironment to be in a low oxygen and low energy state. This hypoxic, low-energy, low-pH microenvironment has a significant impact on the human immune system, which can affect the function of T cells, promote the immune escape of tumor cells, and accelerate the occurrence, development and metastasis of tumor cells[58]. At the same time, the tumor metabolism process will produce immunosuppressive factors, change the function of immune cells, make the tumor microenvironment in an immunosuppressive state, and further accelerate the occurrence of tumors[59].

In the natural immune system, macrophages, as highly plastic cells, play different roles in promoting inflammation and anti-inflammation in the body[60], the transition of macrophages from a pro-inflammatory state to a repair state is crucial for promoting inflammation and restoring homeostasis. It was found that after LPS activated M1 macrophages, their glycolytic metabolism increased and the concentration of lactic acid increased, and the accumulated lactic acid could be used as a precursor to lead to the lactic acid modification of histone lysine. The results showed that histone lactate played an important role in the homeostasis regulation of M1 macrophages infected by bacteria[61−63]. Lactic acid can participate in gene expression regulation through the apparent modification of histone lactate. The high lactic acid produced by aerobic glycolysis is the essential feature of Warburg effect, which suggests that Warburg effect may participate in the occurrence of disease through epigenetic. Therefore, the discovery of histone lactate provides a new idea for Warburg effect to participate in the molecular mechanism of disease occurrence. Studies have observed that lactic acid produced by malignant tumor cells can regulate the activity of dendritic cells, indicating that tumor-derived lactic acid also affects the immune response of anti-tumor T cells[64]. These studies show that lactic acid molecules play an important role in the process of inflammatory regulation and immune homeostasis through the apparent modification of histone lactate. In addition, the accumulation of extracellular lactate has a significant impact on the metabolism of tumor cells and the transformation of non-tumor cells into tumor cells. The promoting effect of lactic acid on tumors includes blocking the differentiation and activation of monocytes and T cells[65]. Research has shown that lactic acid can promote the secretion of vascular endothelial growth factor and the polarization of M2 type macrophages through a hypoxia-inducible factor-1α (HIF-1α) dependent mechanism. Additionally, arginase 1 secreted by polarized M2 type macrophages can transmit signals to tumor cells, promoting the growth of tumor cells[66,67].

Recently, the success of immunotherapy has attracted researchers' attention to the tumor immune microenvironment[68]. There is a close relationship between the key glycolytic enzyme PKM2 and inflammation[69−71]. PKM2 can play an important role in immune metabolism by enhancing oxidative phosphorylation and Warburg effect, and building a bridge between energy metabolism and tumor immunity. Therefore, a comprehensive understanding of the interaction between key glycolytic enzymes and immune cells will help to find potential targets for tumor therapy and provide a new scheme for immunotherapy combined with small-molecule targeted metabolic therapy. Relevant studies

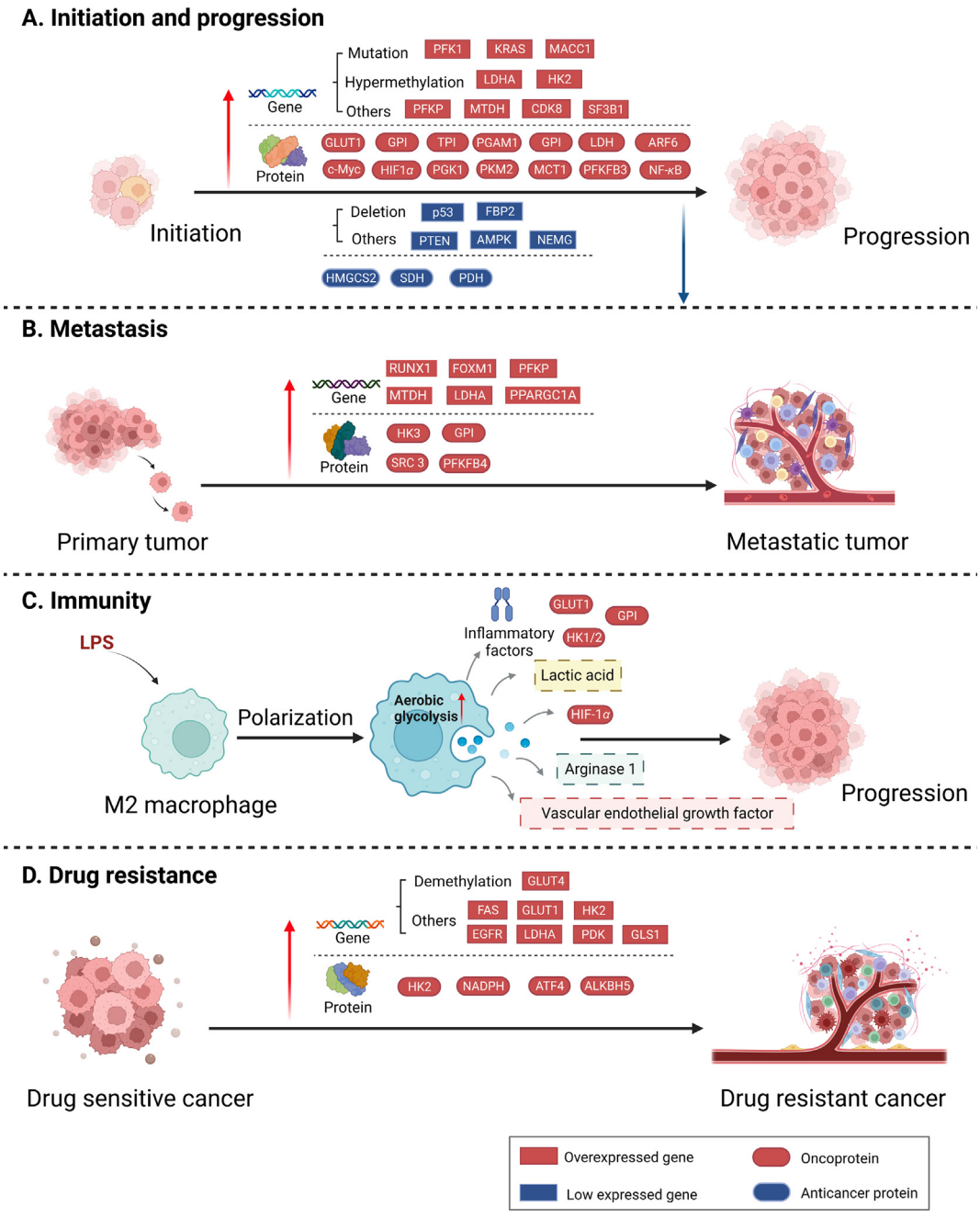


Figure 2 The role of the Warburg effect in cancer. (A) Up-regulation of cancer-promoting factors and down-regulation of tumor suppressor factors enhance the Warburg effect and promote tumor initiation and progression. (B) Up-regulation of cancer-promoting factors and down-regulation of tumor suppressor factors enhanced the Warburg· effect and promoted the metastasis of primary tumors. (C) LPS promotes the polarization of M2 macrophages to produce immune factors and regulate tumor progression. (D). The Warburg effect promotes the transformation of drug-sensitive tumor cells into drug-resistant tumor cells.

have shown that in the treatment of prostate cancer, increasing the infiltration of M2 macrophages in the tumor immune microenvironment, inhibiting the expression of dendritic cells, and increasing the level of immunosuppressive cytokines can improve the efficacy of immunotherapy[72]. In addition, in prostate cancer, as the exposure of tumor cells increases during drug treatment, the tumor microenvironment also changes, making the tumor microenvironment further "evolve" to the immunosuppressive environment, which to some extent explains the reason for the low objective response rate of immune treatment of prostate cancer in the published research[73]. By altering the tumor immune microenvironment to regulate the function of immune cells, we can achieve the goal of anti-tumor treatment, which provides a novel approach to anti-tumor therapy. Therefore, a comprehensive understanding of the interaction between key glycolytic enzymes and immune cells can help identify potential targets for tumor therapy and provide new solutions for immunotherapy combined with small molecule targeted metabolic therapy (Fig. 2C).

3.4. Cancer drug resistance

Tumor resistance seriously affects clinical efficacy and patient prognosis, and is one of the main reasons for the failure of tumor-targeted therapy. The characteristic aerobic glycolysis of tumor cells is one of the important factors affecting targeted drug resistance[74]. Glucose metabolism and glutamine metabolism are significantly up-regulated in tumor cells, providing cells with material synthesis precursors, energy and redox power, which is consistent with the characteristics of rapid tumor proliferation. Many studies have shown that metabolism is related to overcoming drug resistance of tumor. The change of tumor metabolism can enhance the occurrence of drug resistance. With the problems of adverse reactions and drug resistance of traditional anti-tumor drugs becoming increasingly prominent, tumor metabolism, as a long-standing proposition, has become the focus of researchers again. Standardized chemotherapy, endocrine therapy, targeted therapy and other comprehensive treatment can make most cancer patients get different degrees of remission, but the following drug resistance is an important reason for the failure of comprehensive treatment. Elevated aerobic glycolysis levels can provide ample ATP and NADPH for tumor cells to repair DNA damage induced by anti-tumor drugs, facilitate intracellular drug efflux, and repair oxidative damage. This collectively promotes drug resistance in tumor cells under conditions of high aerobic glycolysis[27]. Therefore, it is important to study the characteristics of aerobic glycolysis in order to reverse the drug resistance of cancer.

Currently, researchers have confirmed that increasing aerobic glycolysis levels can enhance drug resistance in various tumor cells[56,75]. Taxus and anthracycline are the most commonly used chemotherapeutic drugs for breast cancer. Simulating the acidic microenvironment resulting from continuous aerobic glycolysis revealed that breast cancer cell MCF-7 exhibited greater resistance to paclitaxel and doxorubicin under acidic conditions (pH 6.6) than under normal culture conditions (pH 7.4)[76]. The production of ATP and lactic acid of MCF-7 decreased after treatment with aerobic glycolysis inhibitor, and the sensitivity to paclitaxel and doxorubicin increased significantly[76]. The weak base property of doxorubicin makes it prone to protonation in the extracellular acidic microenvironment formed by aerobic glycolysis, thus hindering the uptake of drugs by tumor cells. The paclitaxel-resistant breast cancer cell line MDA-MB-435 has higher LDH-A expression level and activity than its parent cells. Suppressing the expression of LDH-A can enhance the drug sensitivity in paclitaxel-resistant cells. Furthermore, the combination of paclitaxel and an LDH-A inhibitor demonstrates a more potent apoptotic effect in paclitaxel-resistant cell lines and other breast cancer cell lines[77]. Endocrine therapy has significantly improved the prognosis of hormone receptor-positive breast cancer patients, but more than 25% of early patients will relapse within 10 years[78]. The isolated cultured breast cancer cell MCF-7 is sensitive to endocrine drugs, while the co-culture of MCF-7 and fibroblasts will show resistance to tamoxifen and fluvastatin. Further research found that the energy coupling relationship between tumor cells and CAFs, namely the reverse Warburg effect, was the main cause of endocrine drug resistance. Utilizing mitochondrial toxic drugs (such as arsenic trioxide and metformin) or tyrosine kinase inhibitors (such as dasatinib) can disrupt this energy coupling, shifting the energy metabolism of MCF-7 towards the Warburg effect and restoring sensitivity to endocrine therapy[79]. This also highlights the important role of tumor microenvironment in the process of drug resistance. Trastuzumab has changed the natural course of HER2-positive breast cancer patients, and is one of the most widely used drugs for targeted treatment of breast cancer, but most patients will have acquired trastuzumab resistance after the initial benefits. Trastuzumab can inhibit the growth of tumor cells by inhibiting the HER2-heat shock factor-1−LDH-A pathway and down-regulating the aerobic glycolysis level of tumor cells. The activation of this pathway leads to the activation of aerobic glycolysis, which is one of the mechanisms contributing to the resistance of HER2-positive breast cancer cells to trastuzumab. The combination of trastuzumab and aerobic glycolysis inhibitor can synergistically inhibit tumor growth in both trastuzumab-resistant and sensitive strains, which may be attributed to stronger aerobic glycolysis inhibition[80].

Numerous studies have shown that aerobic glycolysis is closely related to the development of tumor-targeted drug resistance. The increased activity of tumor aerobic glycolysis can cause an increase in lactate dehydrogenase levels, leading to a weakened effect of anti-tumor immunosuppressive agents. The transport proteins, key rate-limiting enzymes, and metabolites in the aerobic glycolysis process can affect tumor progression and drug resistance through different mechanisms. The mechanism of tumor cell resistance to targeted drugs is very complex and is the result of the interaction of various factors, but the specific mechanism has not been fully elucidated. More and more evidence suggests that the aerobic glycolysis process of tumor cells is closely related to targeted drug resistance. The abnormal aerobic glycolysis process of tumor cells helps them to rapidly proliferate to adapt to nutritional constraints and form drug resistance phenotypes. In future anti-tumor treatment research, targeted glycolytic drugs can be combined with existing anti-tumor targeted drugs, which may help overcome tumor resistance and have significant implications for improving treatment effectiveness (Fig. 2D).

4. Regulators of Warburg effect

4.1. Direct regulatory enzymes

Different subtypes of certain enzymes can promote Warburg effect in different types of cancer, thus inducing cancer development, including GLUT 1/2/3/4, HK 1/2/3, GPI, phosphofructokinase-fructose-bisphosphatase (PFKFB) 3/4, aldolase A (ALDOA), triosephosphate isomerase (TPI), phosphoglycerate kinase 1 (PGK1), phosphoglyceric acid mutase-1 (PGAM1), pyruvate kinase M2 (PKM2), Lactate dehydrogenase (LDH) A/B, monocarboxylate transporter 1 (MCT-1), hexosephosphate isomerase (HPI), PFK-L, aldolase (ALD)-A, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), enolase (ENO)-α[81,82]. Interestingly, a small number of enzymes play an anti-cancer role in inhibiting Warburg effect in cancer, including pyruvate dehydrogenase (PDH), succinate dehydrogenase (SDH), 3-hydroxy-3-methylglutaryl CoA synthase-2 (HMGCS2) (Table 1) (Fig. 3).

4.1.1. Glucose transporter (GLUT)

The GLUT family, composed of 14 transmembrane proteins encoded by *SLC2A* gene, is a carrier protein embedded in the cell membrane. Under the condition of not consuming energy, it regulates the extracellular glucose to enter the cell by promoting diffusion along the concentration gradient[83]. The transformation of energy metabolism mode of tumor cells requires tumor cells to take more glucose to meet the needs of biosynthesis. As a carrier for glucose to enter cells through cell membranes, glucose

transporters play an important role in the process of enhanced aerobic glycolysis of malignant tumor cells[84]. GLUT1, also known as SLC2A1, exists in almost every cell of the human body. It is the most important glucose transporter in brain, nervous system, muscle and other tissues and organs, and is extremely important for maintaining human normal physiological functions. If the function of GLUT1 is completely lost, it will lead to death. Partial loss of function will lead to brain atrophy, mental retardation, growth retardation, epilepsy and other symptoms. On the other hand, GLUT1 also plays an important role in the metabolism of cancer cells. Cancer cells need to consume excessive glucose to maintain their growth and expansion. A significant excess of GLUT1 in cells often means that there is carcinogenesis[85].

Whether in a hypoxia or not, the aerobic glycolysis process in tumors may be driven by HIF-1α, which induces the activity of various enzymes responsible for metabolic switching[81]. HIF-1 increases the expression of a large number of glycolytic enzymes, which are subtypes of glycolytic enzymes found in non-malignant cells. Renal cell carcinoma (RCC) is the most common type of RCC. Because abnormal hypoxia-inducible factor (HIF) stability (HIF-1 or HIF-2) leads to decreased mitochondrial activity, and the inactivation of von Hippel Lindau tumor suppressor gene in RCC, these cells highly rely on glucose uptake mediated by high affinity GLUT1 for aerobic glycolysis and ATP generation, which ultimately drives tumor development[82]. A study found that compound STF-31 selectively kills RCC that depends on GLUT1 by directly binding to GLUT1 and hindering glucose uptake in the body, ultimately inhibiting the growth of RCC without causing toxicity to normal tissues[82]. Glucose transporter isoform GLUT2, also known as Slc2a2, is a glucose transporter that is expressed in liver cells, intestine, kidney and central nervous system. Due to its low affinity and high capacity, it has the ability to promote metabolism and provide metabolites that stimulate the transcription of glucose sensitive genes[86,87]. Some studies have shown that abnormal expression of GLUT2 is closely related to tumorigenesis, and it may eventually cause high expression of GLUT2 in MCF7 and MDA-MB-231 cells and tumor models through functional involvement in fructose metabolism[88]. The high expression of GLUT2 in pancreatic ductal adenocarcinoma (PDAC) also indicates a poor clinical prognosis. GLUT2 depends on the production of p38γ induced aerobic glycolysis to ultimately promote the growth of PDAC[89]. GLUT3, which is highly specifically expressed by neurons, has unique characteristics suitable for cell specific expression and function[90]. Its regulation is an adaptive response, which can prevent cell damage when the metabolic energy of the brain is reduced. As a carrier of glucose entering cells, GLUT3 is one of the important participants in cell glucose metabolism and tumorigenesis, and its high expression is concerned with the low survival rate of tumor patients[91,92]. GLUT3 can be up-regulated by CUEDC2 (CUE domain containing protein 2) to enhance aerobic glycolysis and ultimately drive cancer progression. It is worth noting that glucocorticoid receptor regulates its transcription by binding to GLUT3 proximal promoter region and plays a key role in CUEDC2 mediated *GLUT3* transcription in PLC cells[93].

Glucose transporter type 4 (GLUT4) is expressed in fat and muscle, playing a crucial role in systemic glucose homeostasis[94]. GLUT4 is effectively sequestered in cells during non stimulation. GLUT4 is interfered in insulin resistance and type 2 diabetes, and glucose uptake in muscle and adipose tissue is reduced[95]. The upregulation of GLUT4 to induce aerobic glycolysis would lead to drug resistance of targeted therapy in cancer. A study found that the N^6 methyl adenosine (m6A) demethylase ALKBH5 promotes the m6A demethylation of *GLUT4* mRNA, and increases the stability of *GLUT4* mRNA in a YTHDF2-dependent manner, thereby enhancing aerobic glycolysis in drug-resistant breast cancer cells. At the same time, the expression of ALKBH5 is significantly up-regulated in HER2 HER2-targeted treatment of drug-resistant breast cancer cells, suggesting that targeting the ALKBH5/GLUT4 axis has therapeutic potential for HER2 targeted treatment of refractory breast cancer patients[96]. Krüppel-like transcription factor 8 (KLF8), as a GT box (CACCC) binding double transcription factor, is abnormally expressed in several types of human tumors. Its high expression is significantly related to carcinogenic transformation and tumor progression[97]. KLF8 activates GLUT4 promoter in a dose-dependent manner, and silencing KLF8 expression significantly reduces glucose uptake, lactate secretion and ATP production. GLUT4 may be a potential transcription target of KLF8. KLF8 regulates aerobic glycolysis by targeting GLUT4 and can be used as a new biomarker for tumor survival and potential therapeutic target[98].

4.1.2. *Hexokinase (HK)*

Aerobic glycolysis is a strictly regulated process. Hexokinase is a key enzyme in the glucose metabolism process. It catalyzes the phosphorylation of glucose to 6-phosphate glucose in the first step of aerobic glycolysis, in which HK plays a crucial role. There are five hexokinase isoenzymes found in mammals, HK1, HK2, HK3, HK4 and hexokinase domain containing 1[99,100]. HK1 was mainly distributed in the brain; HK2 was mainly distributed in myocardium, fat and bone; HK3 was mainly distributed in bone marrow, lung and spleen; HK4, also known as glucokinase, regulates insulin secretion in the pancreas and regulates glucose uptake and glycogen synthesis and decomposition in the liver[99]. The five isoenzymes of hexokinase have specific expression levels in different energy metabolism pathways of different tumor cells. These characteristic metabolic pathways provide possibilities for tumor intervention and treatment[101]. The most common mutated oncogene in cancer is KRAS. Carcinogenic KRAS changes tumor metabolism by increasing glucose intake and promoting aerobic glycolysis[102]. KRAS produces two gene products, *KRAS4A* and *KRAS4B*, by using the substitute fourth exon[103]. HK1, as the effector of KRAS4A, can change the activity of HK1 by direct GTP-dependent interaction with KRAS4A[104]. Since HK1 is a glycolytic enzyme controlling the pathway flow, KRAS4A will have a significant impact on the direct regulation of HK1[104]. Relevant studies have designed HK1 inhibitors to target KRAS-mediated metabolic reprogramming[105]. At present, it is generally believed that HK2 has a dual role in tumor cells: one is to induce aerobic glycolysis, and the level of cell aerobic glycolysis is positively correlated with the expression and activity of HK2; The other is to inhibit apoptosis by binding with the volt-dependent anion channel (VDAC) on the outer membrane of mitochondria[106]. Both HK1 and HK2 can directly bind to VDAC. As a mediator of the release of apoptosis promoting proteins, VDAC1 oligomerization reconstructs the outer membrane of mitochondria to change its permeability so that the channel remains closed, and inhibits the release of cytochrome *c* to inhibit mitochondrial-mediated apoptosis[107,108]. HK2 is hardly expressed in normal tissues, but highly expressed in many tumor tissues[109−111]. The expression level of HK2 is often related to the rapid proliferation of tumor cells and the prognosis of tumor patients. Interestingly, glioblastoma (GBM) showed an increase in HK2 expression, therapeutic drug resistance and intracranial

Table 1 Direct regulatory enzymes.

Name	Regulation on Warburg effect	Regulatory mechanism	Cancer type	Ref.
Glucose transporter type 1 (GLUT1)	+	Gluts are glucose transporters on the cell membrane which assistant with glucose entering	Renal cell carcinomas	82
Glucose Transporter 2 (GLUT2)			Pancreatic ductal adenocarcinomas (PDAC)	89
Glucose Transporter 3 (GLUT3)			Hepatocellular carcinoma	93
Glucose Transporter 4 (GLUT4)			Gastric cancer	98
Hexokinase 1	+	Hexokinases change glucose from a stable state to an active state, producing "glucose-6-phosphate"	Pancreatic cancer	104
Hexokinase 2			Glioblastoma multiforme	112
Hexokinase 3			Colorectal cancer	120
Glucose-6-phosphate isomerase	+	Rearrangement of "glucose-6-phosphate" to "fructose-6-phosphate"	Neuroblastoma	127
Phosphofructokinase-1(PFK1)	+	Fructose-6-phosphate is catalyzed to produce fructose-1,6-diphosphate	Osteosarcoma; colon cancer; lung cancer	130
Phosphofructokinase-fructose-bisphosphatase-3 (PFKFB3)	+	PFKFB3 activates PFK1 to regulate aerobic glycolysis	Pancreatic ductal adenocarcinoma	131
6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 (PFKFB4)	+	PFKFB4 catalyzes the kinase reaction that synthesizes F2,6-BP from fructose-6-phosphate (F6P) and ATP, and it can also hydrolyze F2,6-BP into F6P and inorganic phosphate (Pi) through its phosphatase activity	Breast cancer	132
Aldolase A (ALDOA)	+	Catalyzes fructose-1,6-diphosphate to "glyceraldehyde 3-phosphate" and "dihydroxyacetone phosphate"	Osteosarcoma	135
Triosephosphate isomerase (TPI)	+	Catalysis of "dihydroxyacetone phosphate" to "glyceraldehyde 3-phosphate"	Colorectal cancer	137
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	+	Two molecules of "glyceraldehyde 3-phosphate" are oxidized by NAD^+ and GAPDH to generate "1,3-diphosphoglyceric acid".	Breast cancer	138
Phosphoglycerate kinase 1	+	Phosphoglycerate kinase catalyzes the conversion of 1,3-diphosphoglycerate to 3-phosphoglycerate	Liver cancer	139
Phosphoglyceric acid mutase-1 (PGAM1)	+	Phosphoglycerate mutase promotes 3-phosphoglycerate to 2-phosphoglycerate	Non-small cell lung cancer (NSCLC) tissues	143
Pyruvate kinase M2	+	Pyruvate kinase catalyzes phosphoenolpyruvate to produce a molecule of ATP and pyruvate	Cervical cancer; brain tumour	147,148
Lactate dehydrogenase A (LDH A)	+	LDH catalyzes the interconversion between pyruvate and lactate.	Breast cancer	77
Lactate dehydrogenase B (LDH B)			Colorectal adenocarcinoma	155
Pyruvate dehydrogenase (PDH)	−	PDH catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA	Renal cell carcinoma	157
Succinate dehydrogenase (SDH)	−	SDH oxidizes succinic acid to fumaric acid	Renal cell carcinoma	158
3-Hydroxy-3-methylglutaryl CoA synthase-2 (HMGCS2)	−	HMGCS2 controls the synthesis of ketone body β-hydroxybutyric acid	Colon cancer	162
CD147	+	CD147 inhibits the p53-dependent signaling pathway	Hepatic carcinoma	166

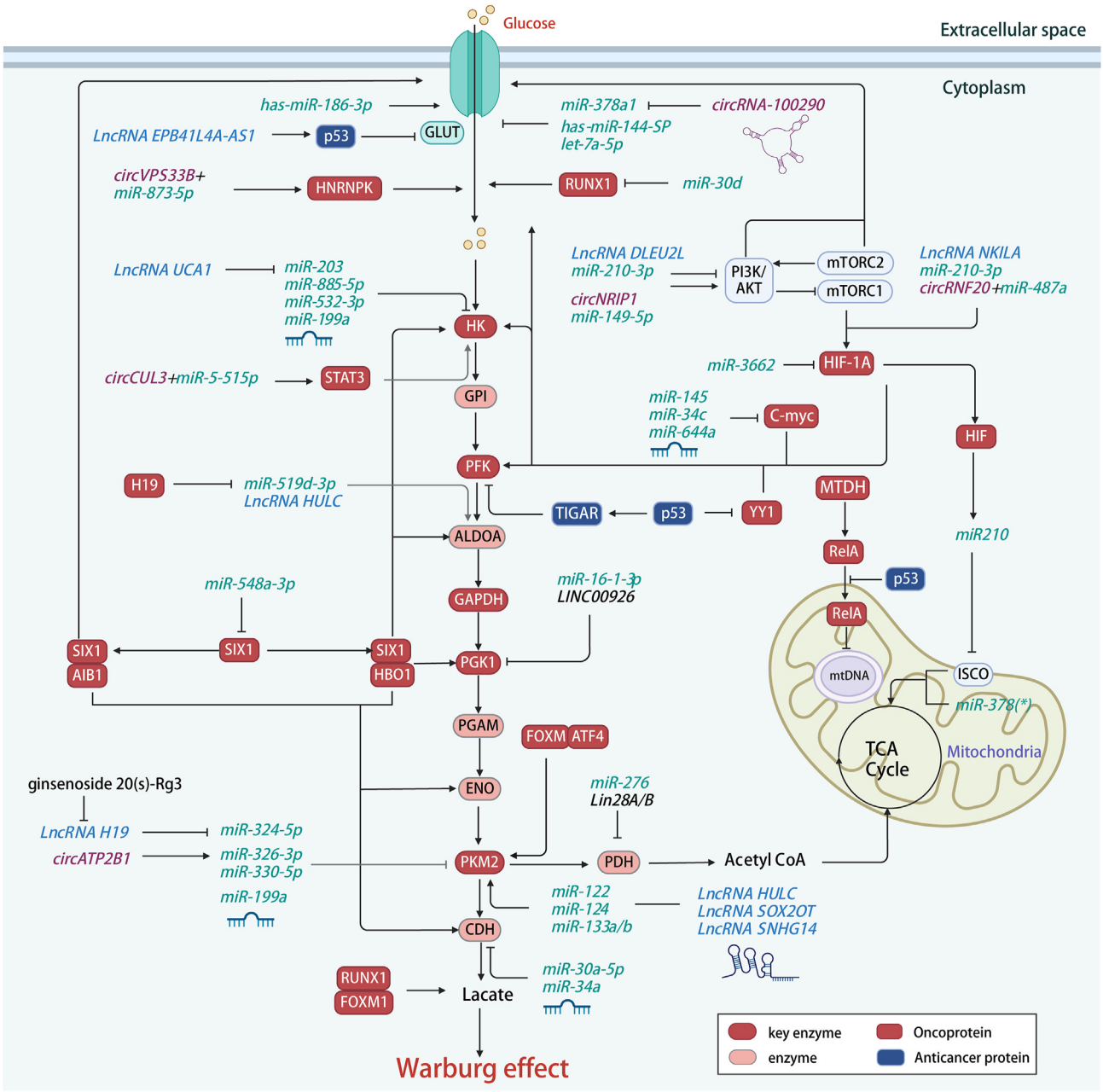


Figure 3 Regulators of the Warburg effect involve lncRNAs, miRNAs, circRNAs, proteins and drugs.

proliferation compared with normal brain and low-grade glioma, which mainly expressed HK1, and was associated with poor overall survival of GBM patients. Intracranial xenografts of HK2 knockout GBM cells showed decreased proliferation and angiogenesis. It is suggested that targeting HK2 may interfere with the growth and therapeutic sensitivity of GBM[112]. Studies have shown that when HK2 from tumor cells, which is bound to mitochondria, is introduced into normal liver cells, it significantly increases the aerobic glycolysis rate, the binding ratio of HK2 to mitochondria, and the affinity of mitochondrial-bound HK2 for the substrate. By capturing ATP released by mitochondria, it becomes one of the mechanisms of tumor high efficiency aerobic glycolysis[113]. In most tumor cells, HK2 protein and its activity significantly increased, ensuring the rapid aerobic glycolysis of tumor cells. The high expression of HK2 protein may be related to gene amplification, expression and regulation. It has been found that activation of HK2 promoter, increase of gene copy number and hypomethylation are important mechanisms of overexpression of HK2 in tumor cells[114]. Hypoxic conditions, cyclicadenosine monophosphate (cAMP) and p53 can enhance the transcription of *HK2* gene[115]. Demethylation of *HK*-related regulatory genes with deoxycytidine and DNA demethylase can increase the expression of HK2 mRNA and protein in rat hepatocytes, indicating that the stability of HK-related regulatory genes can affect the expression of HK2[116]. Insulin can induce *HK2* gene transcription of adipocytes and muscle cells, increase mRNA and promote protein synthesis[117]. The methylation degree of *HK2* gene promoter was significantly different between high glycolytic tumor cells and

normal cells. There were 18 CpG sites methylation of *HK2* gene in normal liver cells, but no methylation of these sites was found in tumor cells, that is, low methylation was closely related to high expression of HK2 in tumor cells[116]. HK1 and HK2 both have an N-terminal hydrophobic 15 amino acid sequence, which is compatible with amphoteric α-helix and can bind to the outer membrane of mitochondria. HK3 and HK4 lack this sequence and cannot bind to the outer membrane of mitochondria[118]. Compared with other HK isoenzymes, HK3 has lower protein expression and higher glucose affinity. Compared with normal tissues, the expression of HK3 in colorectal cancer tissues was up-regulated and positively correlated with some metastasis-related genes[119]. LPS, as a classical inflammatory body activator, can activate inflammatory bodies in cancer cells to enhance metastasis. Its enhanced cancer cell movement depends on the increase of glucose uptake and aerobic glycolysis[120]. In the presence of LPS, NF-κB activated inflammatory bodies upregulate the expression of nuclear Snail, forming a protein complex with Snail, which binds to the promoter region of HK3 to enhance aerobic glycolysis[120]. HK3 was significantly up-regulated under LPS treatment, which could protect cells from oxidant-induced death and increase ATP production under hypoxia[121]. In addition, another key enzyme of aerobic glycolysis, GPI, also performs important functions in cancer. Its inhibition will hinder aerobic glycolysis and activate oxidative phosphorylation. GPI is also called glucose phosphate isomerase or hexose phosphate isomerase, and can also catalyze the exchange of furan isomers of α and β of glucose 6-phosphate. GPI also has the activity of cell division and growth factors *in vitro*, which has the same effect as autocrine motor factor (AMF)[122,123]. Overexpression of GPI/AMF is related to the aggressive phenotype, increased mortality and poor prognosis of many cancer types[124−126]. Valproic acid, as an inhibitor of histone deacetylase (HDAC), can inhibit the progress of neuroblastoma (NB) by inhibiting E2F transcription factor 1 (E2F1)/GPI signal pathway and ultimately blocking Warburg effect[127].

4.1.3. *Phosphofructokinase (PFK)*

The second step of the aerobic glycolysis pathway is that fructose 6-phosphate and ATP are converted into fructose 1,6-diphosphate and ADP under the action of 6-PFK-1, which is also the second irreversible reaction of the aerobic glycolysis pathway. PFK includes two subtypes: PFK-1 and PFK-2. PFK-1 is the most important rate limiting enzyme in the aerobic glycolysis pathway. It is a tetramer, which is regulated by the allosteric regulation of fructose 1,6-diphosphate, ADP, AMP, fructose 2,6-diphosphate, ATP and citric acid. PFK-2 is a bifunctional enzyme with two independent catalytic centers in the enzyme protein, which can act as 6-phosphate fructose kinase 2 to catalyze the phosphorylation of 6-phosphate fructose C2 to form fructose 2,6-diphosphate, and also act as fructose diphosphatase-2 to hydrolyze fructose 2,6-diphosphate C2 to 6-phosphate fructose, thus completing the mutual conversion of fructose 6-phosphate and fructose 2,6-diphosphate. And then realize the regulation of PFK1[128]. Selective inhibition of PFK-1 activity can prevent the proliferation of gastric cancer (GC) cells and inhibit the growth of carcinoma in situ[129]. As a structural homolog of p53, the up-regulation of TAp73 is related to the higher expression of PFKL in tumor cells. By activating the expression of PFK-1/PFK-1, it can enhance glucose consumption and lactate excretion, increase ATP production and enhance antioxidant defense, and promote Warburg effect, which has established that TAp73 may be the key regulator of aerobic glycolysis[130]. Phosphate fructose kinase-fructose diphosphatase-3 (PFKFB3), as a glycolytic driver, can also activate the key rate-limiting enzyme PFK-1. It has the highest kinase activity in the PFKFB family and is overexpressed in PDAC. It may provide local ATP supply in the plasma membrane of PDAC cells to maintain the plasma membrane calcium ATPase function. PFKFB3 inhibitor PFK15 causes cytotoxic calcium overload by inhibiting the function of PMCA, and ultimately leads to cell death. It is suggested that targeted aerobic glycolysis may be a feasible treatment for PDAC[131]. Another regulatory enzyme, fructose-6-phosphate 2-kinase/fructose-2,6-diphosphatase 4 (PFKFB4), which synthesizes glycolytic allosteric stimulators, up-regulates the expression of transketolase in S857 phosphorylated steroid receptor coactivator-3 (SRC-3) to drive glucose flux to purine synthesis. Silencing SRC-3 or PFKFB4 can inhibit the growth and metastasis of breast tumors *in vivo*, suggesting that targeting the PFKFB4−SRC-3 axis may have therapeutic value in breast tumors that are significantly dependent on glucose metabolism[132].

4.1.4. *Others*

Fructose-diphosphate aldolase A (ALDOA) is highly expressed in various types of cancer as a glycolytic enzyme[133,134], especially osteosarcoma (OS)[135]. ALDOA competes with miR-34c-5p and reduces the inhibitory effect of miR-34c-5p on ALDOA, resulting in increased ALDOA expression and aerobic glycolysis. The miR-34c-5p/ALDOA axis may provide a new therapeutic target for OS treatment[135]. TPI can catalyze the mutual conversion of dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate and is highly expressed in tissues with increased aerobic glycolysis ability[136,137]. The regulatory characteristics of GAPDH are the most different in the Warburg effect process. After metabolic control analysis based on the aerobic glycolysis mathematical model, GAPDH showed high computational flux control coefficient and low reaction free energy, suggesting that GAPDH may be involved in controlling the rate of aerobic glycolysis. The natural product koningic acid, as a specific GAPDH inhibitor, showed its ability to dynamically affect aerobic glycolysis in BT-474 tumor bearing mice, The upstream glycolytic metabolites F 1,6-BP and DHAP accumulated to their peak within 500−1000 min, while the downstream glycolytic metabolites 3 PG and PEP were depleted within the first 10 min and subsequently recovered. At the same time, the tumor size of BT-474 tumor bearing mice was significantly inhibited after KA treatment, suggesting that KA can induce the acute dynamic changes of aerobic glycolysis network in tumors, which is the main way to restrain the proliferation of tumors of breast cancer by influencing aerobic glycolysis mechanism[138]. PGK1 is the first enzyme to produce ATP in aerobic glycolysis, which is mediated by different post-translational modifications. *O*-GlcNAc is a universal post-translational modification of protein serine and threonine residues. Compared with adjacent matched tissues, *O*-GlcNA-cyclization of PGK1 is significantly higher in human colon cancer tissues. Blocking the acylation of T255 *O*-GlcNA on PGK1 can inhibit the Warburg effect, reduce the proliferation of colon cancer cells, and inhibit the growth of tumor in nude mice[139] Phosphate glycerate mutase catalyzes the conversion of 3-phosphate glyceride (3-pG) to 2-phosphate glyceride (2-PG) in the late stage of aerobic glycolysis, and its expression can be observed to increase in different cancers[140−142]. In non-small cell lung cancer (NSCLC) tissues, mTOR, as a positive regulator of Warburg effect, stimulates the expression of downstream effector PGAM1 through transcriptional activation mediated by HIF-1α, and

blocks PGAM1's inhibition of mTOR-dependent aerobic glycolysis, which can hinder the occurrence and proliferation of NSCLC[143]. There are four pyruvate kinase subtypes that regulate the final step limit of aerobic glycolysis in mammals[136,144], while tumor tissues only express the embryonic M2 subtype of pyruvate kinase (PKM2)[145,146]. Knocking down PKM2 expression will reduce the production of lactic acid and increase the consumption of oxygen, and ultimately lead to the reversal of Warburg effect[147]. The phosphorylation level of PKM2 S37 is related to the activity of EGFR and ERK1/2 in human GBM samples. Replacing the wild-type PKM2 with a nuclear translocation defect mutant (S37A) can block the Warburg effect promoted by EGFR and the development of brain tumors[148]. It is suggested that PKM2 expression is necessary for aerobic glycolysis. In the cytoplasm of tumor cells, lactate dehydrogenase (LDH) catalyzes the conversion between pyruvate and lactic acid. The tetramer LDH consists of two subunits encoded by independent genes: LDHA and LDHB[149,150]. LDHA controls the conversion of pyruvate to lactic acid during cell aerobic glycolysis in muscle or liver[151]. The promoted expression and activity of LDH-A in paclitaxel-resistant cells are directly related to their sensitivity to oxalate, an aerobic glycolysis inhibitor. The inhibition of LDH-A makes paclitaxel-resistant cells re-sensitive to paclitaxel[77], indicating that LDH-A may be a promising therapeutic target to overcome paclitaxel resistance. Lactate dehydrogenase B controls the conversion of lactic acid to pyruvate in the process of cell aerobic glycolysis in the heart and brain[150,152]. The phosphorylation of LDHB serine 162 mediated by the conservative serine/threonine kinase Aurora-A, which is responsible for the centrosome maturation in G2 and the formation of bipolar spindle in mitosis[153,154], significantly increases its activity of reducing pyruvate to lactic acid, thus promoting NAD regeneration, aerobic glycolysis flux and biosynthesis of glycolytic metabolites, so as to promote tumor progression[155]. Blocking S162 phosphorylation by LDHB-S162A mutant can inhibit aerobic glycolysis and tumor growth in cancer cells and xenotransplantation models[155]. It reveals the interesting mechanism of LDHB in aerobic glycolysis regulation and tumor progression. Metabolic changes are particularly prominent in RCC, especially in clear cell renal cell carcinoma (ccRCC)[156]. Compared to its matched adjacent kidney tissue, ccRCC tumor exhibited enhanced aerobic glycolysis, inhibited PDH activity, and displayed invasive tumor characteristics such as minimal glucose oxidation and turnover of TCA cycle *in vivo*, which provided strong evidence for the Warburg effect in human tumors for the first time[157]. SDH, as the first TCA cycle enzyme with tumor inhibition characteristics, is responsible for the oxidation of succinate to fumarate in the TCA cycle, and sending electrons into the mitochondrial respiratory chain to produce ATP (complex II). Silencing SDH can maintain the maximum glycolytic flux by consuming extracellular pyruvate, thereby preserving Warburg-like bioenergy characteristics, indicating the metabolic vulnerability of SDH-related malignant tumors in the future[158]. HMGCS2 is a rate-limiting enzyme in the pathway of ketone body production, which can lead to the production of ketone bodies including β-hydroxybutyrate and participate in the metabolic reprogramming of tumor cells[159,160]. When the expression of HMGCS2 is reduced, the ketone body production is reduced, which greatly improves the utilization rate of tumor cells for energy *in vivo*, and promotes the metastasis and progression of tumor[149,161,162]. CD147 is a transmembrane protein that is over-expressed on the surface of various malignant cells[163]. Its silencing significantly reduces the aerobic glycolysis rate and lactic acid efflux in cancer cell lines, indicating that CD147 is involved in tumor aerobic glycolysis[164,165]. CD147 activates the PI3K/Akt signal pathway in Hepatocellular carcinoma (HCC) cells through lactic acid output mediated by monocarboxylate transporter 1 (MCT1), up-regulates GLUT1 and down-regulates TIGAR, PGC1a/TFAM and p53R2, and inhibits mitochondrial biogenesis and oxidative phosphorylation in a p53 dependent manner[166]. After blocking CD147 and/or down-regulating MCT1, glucose metabolism decreased and the growth of HCC cells was inhibited[166].

The process of cancer are affected by various factors. GLUTs, key aerobic glycolysis enzymes (such as HKs, PFKs, PKs) and lactic acid production enzymes (such as LDHs) regulate the glucose metabolism in the body and supply energy for human cells. Abnormal enhancement of aerobic glycolysis is one of the important features in tumor growth, during which GLUTs and key glycolytic enzymes participate in energy metabolism of tumor cells, regulating their growth, infiltration, and invasion. Studying the possible effects of changes in key glycolytic enzymes in tumor cells on cell metabolism, revealing their roles and molecular mechanisms in tumor occurrence and development, not only enriches research ideas on tumor related diseases, but also provides new ideas and treatment targets for early diagnosis and treatment of cancer. At the same time, it can also provide new ideas for discovering new tumor treatment drugs.

4.2. *Transcription factors and transcriptional co-regulators*

More than ten genes encoding glycolytic enzymes directly lead to Warburg effect, and transcription factors play a direct role in regulating Warburg effect[150,167,168] (Table 2). Transcription factor sine oculis homeobox 1 (SIX1) is responsible for regulating the occurrence of body organs[169,170]. Its overexpression occurs in various types of cancer and is positively correlated with poor prognosis[170−172]. The up-regulation of SIX1 is usually accompanied by the down-regulation of microRNA-548a-3p. A study found that SIX1 promotes aerobic glycolysis through HBO1 and AIB1 histone acetyltransferase, and is directly inhibited by microRNA-548a-3p[173]. It indicates that targeting microRNA-548a-3p/SIX1 axis may be a new strategy for cancer treatment. Transcription factor Yin Yang 1 (YY1) is a multifunctional transcription factor protein that can activate or inhibit genes[174−176]. It is overexpressed in prostate cancer. By directly binding to and activating the gene *PFKP* encoding glycolytic rate-limiting enzyme, YY1 ultimately enhances the Warburg effect and promotes the malignant growth of prostate cancer[177]. The expression of aerobic glycolysis related-genes *SLC2A1* and *HK1* is positively correlated with the expression of *RUNX1* mRNA. RUNX1 and HK1 serve as adverse prognostic factors for PDAC patients. Overexpression of RUNX1 can increase lactate secretion, glucose uptake, intracellular ATP levels, induce the Warburg effect, and promote tumor growth and metastasis[178]. Fork-head box protein M1 (FOXM1), as a carcinogenic transcription factor of the forkhead transcription factor superfamily, also participates in the regulation of metabolism in cancer[179,180]. It can increase the activity of lactate dehydrogenase, lactate production and glucose utilization by up-regulating the expression of LDHA, and ultimately promote the occurrence and metastasis of pancreatic adenocarcinoma[181]. As a tumor suppressor, p53 participates in metabolism regulation as an important part of p53 response, which not only helps to maintain the dynamic balance of normal cell metabolism, but also helps to control the development of cancer[182]. Transient metabolic stress, such as the fluctuation of

available oxygen and nutrients, will also trigger more adaptive responses involving p53. In this process, p53 induces metabolic remodeling and promotes catabolism, while coordinating to reduce cell proliferation and growth[183,184]. P53 can inhibit Warburg effect by reducing aerobic glycolysis and promoting oxidative phosphorylation through multiple mechanisms[185]. The fructose phosphate enzyme, which promotes the third step of aerobic glycolysis pathway, is regulated by various metabolites in the glucose metabolism mechanism[186]. Its metabolites include ATP, citrate and lactic acid. The fructose phosphate enzyme can directly inhibit PFK1, and PFK1 can be activated by AMP and fructose-2,6-diphosphate. P53 plays a key regulatory role in this signal pathway, that is, p53 reduces the rate of aerobic glycolysis by up-regulating the expression of TIGAR, promotes aerobic glycolysis and transfers its intermediate product to the predetermined pentose phosphate pathway. In addition, p53 has an inhibitory effect on glycolytic enzymes in this pathway[187,188]. In fibroblasts, p53 not only down-regulates the phosphoglyceride mutase that promotes the conversion of glycerol 3-phosphate to glycerol 2-phosphate[189]. In addition, it also has a negative regulatory effect on the expression of pyruvate dehydrogenase 2, which reduces the activity of pyruvate dehydrogenase and further prevents the conversion of pyruvate to acetyl coenzyme A[190]. The co-loss of p53 and p10 will promote tumor development by increasing the selective up-regulation of HK2-mediated aerobic glycolysis by hexokinase HK2[191]. NF-κB is a multi-member nuclear transcription factor that can participate in a variety of biological processes, including cell proliferation and differentiation, immune and inflammatory reactions. The NF-κB protein family consists of five members: ρ50 (NF-κB1), p52 (NF-κB2), p65NF-κB (RelA), c-Rel (Rel) and RelB, among which p65NF-κB (RelA) is the most widely studied member of the NF-κB family. NF-κB is also an important cancer-promoting factor. NF-κB activation can be observed in various types of tumors[192–196]. A variety of carcinogenic factors such as tobacco, alcohol and radiation can cause NF-κB activation, further up-regulate a series of inflammatory factors, and promote cell proliferation and malignant transformation[197]. As an important transcription factor in the process of epithelial-mesenchymal transformation, Snail can up-regulate cellular aerobic glycolysis, thus promoting the occurrence and development of tumors[119,198,199], and it is positively correlated with the expression of the key enzyme HK3 in the first step of aerobic glycolysis and clinical adverse prognosis[199]. Transcription factor NF-κB can directly bind to snail promoter, start snail transcription and up-regulate its protein expression[200]. Some studies have shown that Metadherin (MTDH), as an oncogene, can accelerate the progression of colorectal cancer (CRC) by up-regulating the expression of NF-κB p65 and snail, inducing aerobic glycolysis. Knocking down *MTDH* gene expression may inhibit the occurrence and development of CRC[201]. ATF4 is a gene expression regulator that can respond to various forms of stress[202], and its existence plays a role in the resistance targeted by LDHA. After being knocked down, ATF4 makes melanoma cells sensitive to LDHA inhibitors and inhibits aerobic glycolysis, and finally inhibits tumor cell proliferation[203]. Peroxisome proliferator-activated receptor γ coactivator-1α (PPARGC1A) is a central regulator of mitochondrial metabolism[204]. It can up-regulate the expression of pyruvate dehydrogenase E1α 1 subunit and mitochondrial pyruvate vector 1 to induce the Warburg effect, promote the metastatic transmission of cholangiocarcinoma (CCA) cells, suggesting that blocking the PPARGC1A signal axis may inhibit the metastasis of CCA[205]. A new tumor suppressor, CAB39L, can also inhibit tumor occurrence by promoting LKB1−AMPK−PPARGC1A axis, thus preventing the metabolic transformation driving carcinogenesis[206].

In recent years, it has been found that the metabolic reprogramming of tumor cells is regulated by many different factors, and the regulation of transcription factors on tumor cell metabolic genes is one of the main mechanisms of tumor cell metabolic reprogramming, among which c-Myc, HIF-1, p53, Fox are the most studied in tumor metabolic Reprogramming. This manuscript reviews the regulatory mechanisms of c-Myc, HIF-1, p53, Fox on aerobic glycolysis with a comprehensive view to providing ideas for understanding tumor metabolic reprogramming and its related molecular mechanisms.

4.3. *LncRNAs, miRNAs and circular RNAs*

The molecular mechanism of cancer pathogenesis is gradually clarified, and its molecular changes mainly include: abnormal expression of lncRNAs, miRNAs and circular RNAs, gene mutation, gene amplification, gene translocation, and epigenetic changes. Among them, lncRNAs, miRNAs and circular RNAs play an important role in the occurrence and development of cancer and are of great value in the diagnosis, assessment of disease progression and prognosis judgment of cancer[207]. In this review, we summarized some LncRNAs, miRNAs and circular RNAs that affect the research program of Warburg Effect in the treatment of cancer (Table 3) (Fig. 3).

4.3.1. *LncRNAs*

LncRNAs refer to non-coding RNAs with a length greater than 200 nucleotides. According to the relationship with protein-coding genes, lncRNAs can be divided into five categories: sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intragenic lncRNAs and intergenic lncRNAs[208]. LncRNAs are involved in almost all aspects of gene regulation, such as gene imprinting, epigenetic regulation, transport between nucleus and cytoplasm, splicing and translation of mRNA[208]. So far, more than 3000 lncRNAs have been confirmed to participate in a variety of biological processes, such as chromatin imprinting, cell differentiation and tumor aerobic glycolysis[209], among which the role in tumor genesis and development includes the regulation of tumor cell proliferation, invasion and metastasis[210]

Homo sapiens long intergenic non-protein coding RNA 00926 (*LINC00926*), an lncRNA producing 2.53 kb transcript, negatively regulates the expression of PGK1 by enhancing the ubiquitination of PGK1 mediated by E3 ligase STUB1, inhibits aerobic glycolysis, tumor growth and lung metastasis of breast cancer *in vitro* and *in vivo*, and predicts good clinical results of breast cancer[211]. It suggests that *LINC00926/PGK1* may represent a potential signaling pathway that inhibits the growth and progression of breast cancer. In TNBC, a hypoxia-induced lncRNA *MIR210HG* as a glycolytic regulator can regulate the expression of glycolytic genes and drive the Warburg effect by increasing the translation of *HIF-1α* mRNA, suggesting that *MIR210HG* target may be a potential strategy for the treatment of TNBC patients[212]. LncRNA *ABHD11-AS1* is overexpressed in NSCLC and closely associated with a poor prognosis. M^6A methyltransferase-like 3 (METTL3) enhances the stability and expression of *ABHD11-AS1* transcript through M^6A modification, and promotes NSCLC proliferation by inducing Warburg effect[213]. The expression of lncRNA *HULC* is up-regulated in hepatocellular carcinoma[214], and as a bridging molecule, it can directly bind with LDHA and

Table 2 Transcription factors and transcriptional co-regulators.

Name	Classification	Regulation on Warburg effect	Regulatory mechanism	Cancer type	Ref.
Six1	Tumor promoter	+	Six1 promotes HBO1 and AIB1 histone acetyltransferases activation thus to increases the expression of many glycolytic genes	Breast cancer	173
Yin yang 1 (yy1)	Tumor promoter	+	Yy1 directly binds and activates PFKP to stimulate aerobic glycolysis	Prostate cancer	177
Runx1	Tumor promoter	+	Runx1 binds to the promoters of SLC2A1 and HK1 to up-regulate their expression to enhance aerobic glycolysis	Pancreatic ductal adenocarcinoma	178
Forkhead box protein M1 (FOXM1)	Tumor promoter	+	FOXM1enhances aerobic glycolysis *via* transcriptional regulation of LDHA expression	Pancreatic cancer	181
P53	Tumor suppressor	−	1. p53 inhibits the expression of glycolytic genes, such as HK2, PGM and GLUT; 2. p53 induces expression of TIGAR (TP53-induced aerobic glycolysis and apoptosis regulator) to decrease fructose-2,6-bisphosphate levels to inhibit aerobic glycolysis		185
NF-κB	Tumor promoter	+	MTDH up-regulates the expression of NF-κB p65 and snail, induces the Warburg effect	Colorectal cancer	201
Atf4	Tumor promoter	+	ATF4 regulates SLC1A5 to increase uptake of glutamine and essential amino acid, thus to activate mTORC1-regulated aerobic glycolysis	Malignant melanoma	203
Steroid receptor coactivator-3 (SRC-3)	Oncogenic transcriptional coregulator	+	The phosphorylation of SRC-3 by PFKFB4 enhances the expression of transketolase, adenosine monophosphate deaminase 1 (AMPD1), and xanthine dehydrogenase to contribute to the Warburg effect	Breast cancer	132
Krüppel-like transcription factor 8 (KLF8)	Tumor promoter	+	KLF8 activated the GLUT4 promoter activity to enhance GLUT4 expression	Gastric cancer	98
Peroxisome proliferator-activated receptor gamma coactivator 1α (PPARGC1A)	Tumor promoter	−	PPARGC1A enhances pyruvate oxidation metabolism through pyruvate dehydrogenase E1 alpha 1 subunit and mitochondrial pyruvate carrier up-regulation to reverse the Warburg effect	Cholangiocarcinoma (CCA).	205
	Tumour suppressive transcriptional co-activator	−		Gastric cancer	206

PKM2 and increase their phosphorylation to promote aerobic glycolysis and enhance the proliferation of hepatocellular carcinoma cells[215]. LncRNA *KCNQ1OT1* is up-regulated in a variety of tumors[216,217]. It enhances aerobic glycolysis and promotes cancer progression by stabilizing HK2 in CRC[218]. Interestingly, another kind of lncRNA *SNHG14* is overexpressed not only in many kinds of cancers[219,220], but also in ischemic brain tissue[221]. In glioma, *Lin28A* can stabilize *SNHG14* and its simultaneous overexpression[222]. The up-regulation of *SNHG14* will promote the degradation of *IRF6* mRNA, further promote the transcription of *PKM2* and *GLUT1*, and finally induce aerobic glycolysis and glioma cell proliferation. It shows the potential strategy of targeting *Lin28A/SNHG14/IRF6* axis to regulate Warburg effect in the treatment of glioma[222]. The cancer genome map database also found that another kind of lncRNA *NKILA* was overexpressed in glioma patients, and its expression level was negatively correlated with the survival time of patients[223−225]. NF-κB interacting lncRNA *NKILA* enhanced the Warburg effect and angiogenesis of glioma by up-regulating HIF-1α expression *in vivo* and *in vitro*, and stimulated the growth of glioma. It suggests that *NKILA* may be a potential target for glioma. Also acting as tumor promoters are lncRNA *IDH1-AS1* and *lincRNA-P21*, which also promote the progression of cancer by promoting aerobic glycolysis[226,227]. Interestingly, lncRNA *EPB41L4A-AS1* as a tumor suppressor can induce p53 and PGC-1α, its down-regulation and deletion are related to the poor prognosis of cancer patients. Knocking down *EPB41L4A-AS1* can promote aerobic glycolysis and glutamine metabolism[228]. Apart from inducing the Warburg effect to promote tumor cell proliferation, lncRNAs can also facilitate tumor metastasis. In HCC cells, lncRNA *SOX2OT* promotes tumor metastasis through PKM2-mediated aerobic glycolysis[229]. LncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) enhances mTOR-mediated TCF7L2 translation to regulate cancer glucose metabolism, inhibit gluconeogenesis and promote aerobic glycolysis, and ultimately promote HCC progression[230].

4.3.2. *miRNAs*

As endogenous non-coding RNAs that regulate gene expression after mRNA transcription, miRNAs participate in numerous physiological and pathological processes, including cell proliferation, apoptosis and differentiation[231]. miRNAs play a crucial role in regulating the glucose metabolism of cancer cells. They mainly target genes that regulate metabolism, change the metabolism of cancer cells, and promote the growth, proliferation and metastasis of cancer cells[232].

Disorder of miRNA expression can cause various types of cancer. As a tumor suppressor, *miR-124* is down-regulated in most patients with CRA or CRC and plays a role in the development of adenoma[233]. Overexpression of *miR-124* can induce autophagy and apoptosis through PTB1/PKM1/PKM2 feedback cascade to participate in the proliferation and development of CRC[233]. In addition, *miR-122*, *miR-133a* and *miR-133b* can also participate in the apoptosis of CRC cells by regulating the reprogramming of M2 pyruvate kinase isoenzyme and metabolism[234]. The OS of RCC patients is positively correlated with the level of *has-miR-144-5p* and negatively correlated with the level of has-miR-186−3p. They may balance the glycolytic state of RCC by regulating GLUT1[235]. PGK1 is over-expressed in many types of cancer, including breast cancer, and is related to poor prognosis[236−238]. *MicroRNA-16-1-3p* inhibits the growth and metastasis of breast tumors by inhibiting the Warburg effect mediated by PGK1[239]. GLUT12 is also up-regulated in breast cancer and promotes glucose uptake[240]. *Let-7a-5p*, as a tumor suppressor[241−243], can inhibit the Warburg effect by inhibiting the expression of GLUT12, and ultimately inhibit the growth and metastasis of breast cancer[244]. The expression of *miR-378* (*) as a molecular switch also affects the occurrence and development of breast cancer. *MiR-378* targets the mRNA of *ERR*γ and *GABPA* at the same time, affects its ability to encode energy metabolism, accelerates the process of tricarboxylic acid circulation, reduces cell oxygen consumption, and ultimately enhances the proliferation of breast cancer cells[245]. *MiR-30a-5p* and *miR-34a* interfere with aerobic glycolysis to treat breast cancer and cervical cancer by inhibiting the expression of LDHA[246,247]. *MiRNA-27b* also plays an anti-cancer role in breast cancer by targeting multiple tumor suppressor genes as a carcinogenic miRNA[248−250]. Glucose metabolism disorder is often related to the abnormal function of PDH complex components, and its expression level is positively related to the survival rate of breast cancer patients[251,252]. *MicroRNA-27b* reduces mitochondrial oxidation and promotes extracellular acidification by inhibiting PDHX, resulting in cell metabolic disorder and promoting the proliferation of breast cancer[252]. *MiR-155* promotes Warburg effect in the development of breast cancer by up-regulating HK2[253]. TNBC is the subtype with the worst prognosis in breast cancer and shows high metabolic remodeling[254]. The cancer genome map data showed that the key regulator *miR-210-3p* in TNBC related to aerobic glycolysis promoted aerobic glycolysis, induced Warburg effect and reduced TNBC cell apoptosis by regulating the downstream aerobic glycolysis genes of HIF-1α and p53[255]. As a carcinogenic miRNA, *miR-214* is up-regulated in different cancers and is induced by hypoxia, its expression level is related to distant metastasis[256−260]. *MiR-214* promotes aerobic glycolysis by targeting adenosine A2A receptor (A2AR) and PR/SET domain 16, and ultimately improves the migration and proliferation of cancer cells[261]. In addition to inducing the Warburg effect, which plays a carcinogenic role in the occurrence and development of cancer, miRNAs can also serve as tumor suppressors for cancer treatment. Interestingly, *miR-3662* inhibits Warburg effect by targeting HIF-1α[262]. *MiR-885-5p* and *miR-532-3p* inhibit the progression of liver cancer and ovarian cancer by silencing HK2 negatively regulating Warburg effect, respectively[263,264]. The liver is the primary organ responsible for regulating the metabolism and energy homeostasis of the whole body, and its abnormal energy metabolism may be closely related to the progress of liver cancer. *MiR-199a* targets both HK2 and PKM2 to limit the aerobic glycolysis process for the treatment of hepatocellular carcinoma[265,266]. The expression of *miR-23a* in HCC mouse model and primary human HCC is up-regulated, and its activation can inhibit PGC-1α and G6PC in a targeted manner, resulting in the accumulation of G6P to produce ribose-5-phosphate for nucleotide synthesis through hexose monophosphate shunt pathway, which can meet the nutrition required for the division and growth of liver cancer cells under hypoxia conditions, and promote the development of liver cancer[267]. *MiR-338-3p* inhibits the expression of PKLR to alleviate the Warburg effect inhibiting the progression of liver cancer[268]. C-MYC oncogene can produce c-Myc protein, which regulates miRNA and glucose metabolism enzymes and ultimately promotes cell proliferation[269,270]. The expression of *miR-23a/b* in human prostate cancer is significantly down-regulated[271]. c-MYC regulates glutaminase through transcriptional inhibition of *miR-23a/b*, up-regulates glutamine catabolism, and promotes the occurrence of cancer[272]. *MiR-145* inhibits *miR-133b*/PKM2

Table 3 LncRNAs, miRNAs and Circular RNAs.

Name	Classification	Regulation on Warburg effect	Regulatory mechanism	Cancer type	Ref.
KCNQ1OT1	Oncogenic lncRNA	+	*KCNQ1OT1* sponges *miR-34c-5p* to increase ALDOA expression to contributed to the Warburg effect	Osteosarcoma	135
miR-34c-5p	Tumor-suppressive miRNA	−	*miR-34c-5p* inhibits ALDOA expression by directly targeting its 3′UTR.	Osteosarcoma	135
miR-30d	Tumor-suppressive miRNA	−	*miR-30d* suppresses aerobic glycolysis by inhibits RUNX1/SLC2A1/HK1 to suppress aerobic glycolysis	Pancreatic ductal adenocarcinoma	178
LINC00926	Tumor-suppressive lncRNA	−	*LINC00926* negatively regulates PGK1 expression to inhibit aerobic glycolysis	Breast cancer	211
MIR210HG	Oncogenic lncRNA	+	*MIR210HG* potentiates the translation of HIF-1α, thus to increase HIF-1α protein level to up-regulate the expression of glycolytic enzymes.	Triple-negative breast cancer (TNBC).	212
ABHD11-AS1	Oncogenic lncRNA	+	*ABHD11-AS1* increases the occupation of EZH2 and H3K27me3 on KLF4 promoter region to enhance KLF4 expression to promoted the Warburg effect	Non-small-cell lung cancer	213
HULC	Oncogenic lncRNA	+	*HULC* directly binds to two glycolytic enzymes, LDHA and pyruvate kinase M2 to promote aerobic glycolysis	Liver cancer	215
KCNQ1OT1	Oncogenic lncRNA	+	*KCNQ1OT1* directly binds and stabilizing HK2 to promote aerobic glycolysis	Colorectal cancer	218
SNHG14	Oncogenic lncRNA	+	*SNHG14* increases IRF6 mRNA degradation and inhibits the expression of IRF6 to encourage aerobic glycolysis	Glioma	222
SOX2OT	Oncogenic lncRNA	+	*SOX2OT* promotes the expression of PKM2 to promote aerobic glycolysis	Hepatocellular carcinoma (HCC)	229
NF-kappa B interacting long noncoding RNA (NKILA)	Oncogenic lncRNA	+	*NKILA* increases the expression of HIF-1α to enhance the Warburg effect	Glioma	225
IDH1-AS1	Oncogenic lncRNA	+	*IDH1-AS1* promotes c-Myc collaborate with HIF1α to activate the Warburg effect	Cervical cancer	226
lincRNA-p21	Oncogenic lncRNA	+	*LincRNA-p21* promotes HIF-1α accumulation to enhance aerobic glycolysis	Cervical cancer	227
EPB41L4A-AS1	Tumor-suppressive lncRNA	−	*EPB41L4A-AS1* interacts and co-localizes with HDAC2 in nucleolus and inhibits the released HDAC2 from nucleolus to hinder aerobic glycolysis	Cervical cancer	228
MALAT1	Oncogenic lncRNA	+	*MALAT1* activates the mTORC1−4EBP1 axis to reprogram the tumor glucose metabolism	Hepatocellular carcinoma	230
miR-124	Tumor-suppressive miRNA	−	Targets polypyrimidine tract-binding protein 1 to block the PKM1/PKM2 regulated aerobic glycolysis	Colorectal cancer	233
hsa-miR-144-5p	Tumor-suppressive miRNA	−	*hsa-miR-144-5p* inhibits GLUT-1 expression	Renal cell carcinoma	235
hsa-miR-186-3p	Oncogenic miRNA	+	*hsa-miR-186-3p* increases GLUT-1 expression	Renal cell carcinoma	235
miR-16-1-3p	Tumor-suppressive miRNA	−	*miR-16-1-3p* suppresses aerobic glycolysis *via* inhibition of PGK1	Breast cancer	239
let-7a-5p	Tumor-suppressive miRNA	−	*let-7a-5p* inhibits GLUT12 expression to suppress aerobic glycolysis	TNBC	244
*miR-378**	Oncogenic miRNA	+	*miR-378** inhibits the expression of ERRγ and GABPA	Breast cancer	245

(*continued on next page*)

Table 3 (*continued*)

Name	Classification	Regulation on Warburg effect	Regulatory mechanism	Cancer type	Ref.
			to increase aerobic glycolysis		
miR-30a-5p	Tumor-suppressive miRNA	−	*miR-30a-5p* inhibits LDHA expression to disturb aerobic glycolysis	Breast cancer	246
miR-34a	Tumor-suppressive miRNA	−	*miR-34a* inhibits LDHA expression to disturb aerobic glycolysis	Cervical cancer	247
miRNA-27b	Oncogenic miRNA	+	*miR-27b* inhibits pyruvate dehydrogenase protein X to contribute to the Warburg effect	Breast cancer	252
miR-155	Oncogenic miRNA	+	*miR-155* upregulates HK2 to contribute to Warburg effect	Breast cancer	253
miR-210-3p	Oncogenic miRNA	+	*miR-210-3p* contributes to maintain HIF-1α stabilization and suppressed p53 activity to strengthen the Warburg effect	TNBC	255
miR-214	Oncogenic miRNA	+	miR-214 targets the adenosine A2A receptor (A2AR) and PR/SET domain 16 to enhance the Warburg effect	Gastric cancer	261
miR-3662	Tumor-suppressive miRNA	−	*miR-3662* dampened aerobic glycolysis by targeting HIF-1α	Hepatocellular carcinoma	262
miR-885-5p	Tumor-suppressive miRNA	−	*miR-885-5p* directly targets the 3′ UTR of HK2 to inhibit its expression	Hepatocellular carcinoma	263
miR-532-3p	Tumor-suppressive miRNA	−	*miR-532-3p* inhibits aerobic glycolysis by targeting HK2	Ovarian cancer	264
miR-199a	Tumor-suppressive miRNA	−	*miR-199a* limits aerobic glycolysis by targeting HK2 and PKM2	Hepatocellular carcinoma	265, 266
miR-23a	Oncogenic miRNA	−	*miR-23a* directly targets PGC-1α and G6PC to decrease the glucose production	Hepatocellular carcinoma	267
miR-338-3p	Tumor-suppressive miRNA	−	*miR-338-3p* suppresses the Warburg effect *via* PKLR inhibition	Hepatocellular carcinoma	268
miR-23a/b	Oncogenic miRNA	+	*miR-23a/b* controls the mitochondrial glutaminase expression to regulate the Warburg effect	Prostate cancer	272
miR-145	Tumor-suppressive miRNA	−	*miR-145* enhance the c-myc/DNMT3A/miR-133b/PKM2 pathway to inhibit the Warburg effect	Ovarian cancer	273
miR-133b	Tumor-suppressive miRNA	−	*miR-133b* inhibits its target gene PKM2 expression to impede the Warburg effect	Ovarian cancer	273
miR-644a	Tumor-suppressive miRNA	−	*miR-644a* directly targets c-Myc, Akt, IGF1R, and GAPDH to inhibit their expression thus to suppress the Warburg effect	Prostate cancer	274
miR-34c	Tumor-suppressive miRNA	−	*miR-34c* suppresses c-Myc expression to inhibit the Warburg effect	Glioblastoma	275
let-7	Tumor-suppressive miRNA	−	*let-7* inhibits PDK1 protein expression *via* post-transcriptional regulation	Hepatoma	282
circRNF20	Oncogenic Circular RNA	+	*circRNF20* acts as the sponge of *miR-487a* to increase HIF-1α expression	Breast cancer	286
miR-487a	Tumor-suppressive miRNA	−	*miR-487a* inhibits the Warburg effect through HIF-1α-HK2 inhibition.	Breast cancer	286
circRNA_100290	Oncogenic Circular RNA	+	*circRNA_100290* sets GLUT1 free from *miR-378a-*	Oral squamous cell carcinoma	288

			mediated GLUT1 inhibition		
miR-378a	Tumor-suppressive miRNA	−	*miR-378a* inhibits GLUT1 expression to obstruct aerobic glycolysis	Oral squamous cell carcinoma	288
circNRIP1	Oncogenic Circular RNA	+	*circNRIP1* acts as a *microRNA-149-5p* sponge to activate AKT1/mTOR pathway	Gastric cancer	293
miR-149-5p	Tumor-suppressive miRNA	−	*miR-149-5p* inhibits the AKT1/mTOR pathway to suppress aerobic glycolysis	Gastric cancer	293
circVPS33B	Oncogenic Circular RNA	+	*circVPS33B* accelerates the Warburg effect *via miR-873-5p*/HNRNPK axis	Gastric cancer	298
miR-873-5p	Tumor-suppressive miRNA	−	*miR-873-5p* inhibits HNRNPK expression to suppress aerobic glycolysis	Gastric cancer	298
circATP2B1	Oncogenic Circular RNA	+	*circATP2B1* accelerates aerobic glycolysis *via* miR-326 thus to activate pyruvate kinase M2	Gastric cancer	301
miR-326	Tumor-suppressive miRNA	−	*miR-326* decreases the expression of PKM2 to bother aerobic glycolysis	Gastric cancer	301
circCUL3	Oncogenic Circular RNA	+	*circCUL3* sponges *miR-515-5p* to activate STAT3−HK2 pathway	Gastric cancer	302
miR-515-5p	Tumor-suppressive miRNA	−	*miR-515-5p* decreases STAT3 expression thus to inhibit HK2 expression	Gastric cancer	302
circFOXP1	Oncogenic Circular RNA	+	*circFOXP1* increases *PKLR* mRNA level to enhance the Warburg effect	Gallbladder cancer	305
miR-370	Tumor-suppressive miRNA	−	*miR-370* decreases *PKLR* mRNA level	Gallbladder cancer	305
circECE1	Oncogenic Circular RNA	+	*CircECE1* interacts with c-Myc to prevent c-Myc ubiquitination and degradation	Osteosarcoma	308
miR-324-5p	Tumor-suppressive miRNA	−	*miR-324-5p* decreases PKM2 expression to enhance the Warburg effect	Ovarian cancer	317
lncRNA-NEAT1	Oncogenic lncRNA	+	*lncRNA-NEAT1* inhibits *miR-34a* to promote LDHA-aerobic glycolysis axis	Cervical cancer	324
miR-34a	Tumor-suppressive miRNA	−	*miR-34a* inhibits LDHA activity to impede aerobic glycolysis	Cervical cancer	324
UCA1	Oncogenic lncRNA	+	*UCA1* elevates the activation of HK2 oncogenes *via* inhibition of miR-203 activity	Esophagal cancer	328
miR-203	Tumor-suppressive miRNA	−	*miR-203* suppress HK2 expression to inhibit glucose uptake	Esophagal cancer	328

pathway by targeting c-myc/DNMT3A pathway in ovarian cancer cells, and jointly inhibits aerobic glycolysis[273]. Also, *miR-644a* and *miR-34c* are tumor suppressors that inhibit Warburg effect by targeting c-myc[274,275]. As one of the cancers with high aerobic glycolysis rate, PDAC is highly sensitive to miRNAs that affect Warburg effect[276,277]. YT521-B homology domain containing protein YTHDC1 can regulate mRNA splicing to promote the decay of *pri-miR-30d* and induce the activation of *miR-30d*[178]. The interaction between *miR-30d* and transcription factor RUNX1 subsequently down-regulated the expression of SLC2A1 and HK1 to inhibit aerobic glycolysis, suggesting that *miR-30d*, as a tumor suppressor, is related to the prognosis of PDAC, and can be used as a potential target and effective prognostic marker for research[178]. The RNA-binding protein Lin28A and its homologue Lin28B target PDK1 in an anoxic or HIF-1-independent manner by regulating the PI3K-mTOR pathway mediated by *let-7*[278], one of the first miRNAs found in *Caenorhabditis elegans*[279−281], and finally enhance the aerobic glycolysis of cancer cells *in vivo* and promote the proliferation of tumor cells[282]. It provides a potential strategy for the treatment of cancer with abnormal expression of Lin28 and *let-7*.

4.3.3. Circular RNAs

CircRNA is a kind of closed circular RNA formed by reverse splicing of exon or intron, which widely exists in human cells and is highly conservative in different species, but has its specificity in different tissues, different developmental stages and different diseases. Due to its unique ring structure, lack of 5′ terminal cap and 3′ terminal poly A tail, and it is not easy to be degraded by exonuclease RNaseR, making circRNA has unique advantages in the development and application of new clinical markers. In addition, more and more evidence show that circRNA, like mRNA and lncRNA, is rich in a large number of microRNA (miRNA) binding sites, which can be used as a miRNA sponge to participate in the competitive endogenous RNA (ceRNA) regulatory network, regulate the expression of downstream target genes, and then participate in the regulation of the occurrence and development of various human diseases including cancer[283−285]. A large number of studies have shown that circRNA plays an important role in the occurrence and development of many clinical common tumors by posttranscriptional regulation of miRNA and/or lncRNA.

CircRNA microarray sequencing in breast cancer samples showed that *circRNF20* transcript was up-regulated and associated with poor prognosis[286]. *CircRNF20*, as a miRNA sponge, carries *miR-487a* to target and promote the promoter binding of HIF-1α and HK2, promote the transcription and expression of HK2, and promote the proliferation of breast cancer cells by inducing Warburg effect[286]. In oral squamous cell carcinoma, the expression of GLUT1 and *hsa_circRNA_100290* (*circ_SLC30A7*) was significantly up-regulated, and the expression of *miR-378a* was significantly down-regulated[287,288]. *MiR-378a* can directly target and bind *circRNA100290* and GLUT1. As ceRNA, *circRNA_100290* can counteract the inhibition of GLUT1 mediated by *miR-378a*, thus inducing Warburg effect and promoting the proliferation of cancer cells[288]. It is possible that the targeted regulation of *circRNA*_100290/miR-*378a*/GLUT1 axis is a potential strategy for oral squamous cell carcinoma. AKT/mTOR pathway, as a classical signal pathway that mediates tumor metabolic homeostasis, promotes tumor growth and metastasis by inducing Warburg effect to maintain energy homeostasis[289−292]. *CircNRIP1* as *microRNA-149-5p* sponge can promote the proliferation, migration and invasion of gastric cancer through AKT1/mTOR pathway[293]. As a DNA-RNA binding protein, the overexpression of heterogeneous nuclear ribonucleoprotein K (HNRNPK) is related to the poor prognosis of various types of cancer[294−297]. *CircVPS33B*, which is up-regulated in invasive GC, as a sponge of *miR-873-5p*, can increase the expression of HNRNPK, promote glucose uptake and lactate production, induce Warburg effect, and promote the growth of invasive GC[298]. PKM2, as the rate-limiting enzyme of aerobic glycolysis, can promote the glucose uptake of tumor cells[299,300]. The up-regulated *circATP2B1* expressed in GC targets *miR-326-3p/miR-330-5p* in the RNA-induced silencing complex dependent manner, reducing their inhibition of PKM2, promoting the aerobic glycolysis process, and enhancing the growth and proliferation of GC[301]. In other studies, the overexpression of a novel type of *circCUL3* was identified in GC through circRNA microarray analysis and qRT-PCR experiment[302]. *CircCUL3* acts as a sponge for *miR-3-515p*, leading to the activation of signal transducer and activator of transcription 3 (STAT3), which then accelerates the transcription process of the key rate-limiting enzyme HK2 in aerobic glycolysis, ultimately triggering the Warburg effect and promoting the development of GC[302]. Because of the heterogeneity and lack of effective markers, most patients with gallbladder cancer (GBC) are in advanced stage when diagnosed[303,304]. Some researchers found that *circFOXP1* overexpressed in GBC as a key regulator of Warburg effect is also a prognostic biomarker of GBC progression[305]. *CircFOXP1* can stabilize *PKLR* mRNA by promoting the nuclear cytoplasmic shuttle of PTBP1 or acting as a sponge of *miR-370*, and up-regulate its expression to regulate Warburg effect and promote GBC progress[305]. Interestingly, circRNA can still act as a reused signal pathway regulator in gene expression without relying on acting as a miRNA sponge[306,307]. The up-regulated expression of *CircECE1* in OS inhibits the transcription of thioredoxin binding protein, a negative regulator of aerobic glycolysis, by activating the proto-oncogene c-Myc, and finally regulates the Warburg effect to promote the occurrence and development of OS[308].

4.3.4. Crosstalk among the lncRNAs, miRNAs and circular RNAs

The *miR-210* derived from pancreatic cancer stem cells has been identified as a carcinogenic miRNA that can enhance the resistance of cancer cells to GEM[309]. *DLEU2L*, as the ceRNA of *miR-210-3p*, is expressed at a low level in pancreatic cancer tissue. It can down regulate its expression by combining with *miR-210-3p*, block AKT/mTOR signal transduction and inhibit Warburg effect, and finally inhibit the proliferation, migration and invasion of pancreatic cancer cells[310]. H19, one of the most extensively characterized lncRNAs related to tumor progression, is overexpressed in various tumors and functions as an oncogene[311−315]. H19 can promote glucose consumption and lactic acid production by inhibiting *miR-519d-3p*/LDHA axis in GC, induce aerobic glycolysis, accelerate proliferation and immune escape of GC cells[316]. It suggests that targeting the *H19*/miR-*519d-3p*/LDHA axis may be an effective strategy for the treatment of GC. H19 can also directly bind with *miR-324-5p* and inhibit it. An active saponin monomer, ginsenoside 20(*S*)-Rg3, extracted from red ginseng, can block H19's competitive inhibition of *miR-324-5p*, further enhance the inhibition of PKM2, and finally inhibit the Warburg effect and hinder the occurrence of ovarian cancer cells[317]. LncRNA *nuclear-rich transcripts 1* (*NEAT1*) plays carcinogenic roles in different types of tumors as tumor promoters[318−323]. Interestingly, *NEAT1* is positively correlated with 5-Fu resistance in cervical cancer. The up-regulated

expression of miR-34a can knock down NEAT1, bind with LDHA and inhibit the rate of cell aerobic glycolysis, and finally sensitize 5-Fu resistant cervical cancer cells[324]. Esophageal cancer (EC), one of the five deadliest cancers[325], is often characterized by early diagnosis, late invasion and dysphagia[326,327]. The expression of lncRNA urothelial carcinoma associated 1 (*UCA1*) was up-regulated in EC, positively correlated with HK2, and negatively correlated with miR-203 expression[328]. The overexpression of *UCA1* can promote the activation of HK2 oncogene by inhibiting the activity of miR-203, improve the glucose uptake rate and produce lactic acid, induce Warburg effect and promote the development of EC[328].

4.4. Oncogenic protein/tumor suppressor

Mitochondria, as the central platform of cell metabolism, can provide the ATP needed by cancer cells to meet capacity requirements[329,330]. Warburg effect is often accompanied by mitochondrial imbalance or dysfunction[331,332]. Compared with normal tissues, hypoxia activated E3 ligase SIAH2 in breast cancer tissues degrades NRF1, downregulates the expression of nuclear-encoded mitochondrial gene, which is related to poor clinical prognosis, thus enhancing aerobic glycolysis[333]. HIFs, a key factor in the adaptive response of cells to hypoxia, can up-regulate the genes encoding metabolic pathway enzymes[334−336], and the overexpression of HIFs is often associated with high aerobic glycolysis and poor clinical prognosis[337−341]. It can increase the production of anaerobic ATP and inhibit tumor cell death through metabolic reprogramming[342−344]. Rho-related BTB domain-containing protein 3 (RHOBTB3), as a novel scaffold protein, is an important ATPase[345], which can promote the degradation of HIFα under the condition of hypoxia or not, thus inhibiting the aerobic glycolysis process and inhibiting the development of tumor[346]. In addition, SIRT3, the main mitochondrial deacetylase in the Sirtuins family[347], inhibits aerobic glycolysis by inhibiting HIF1α-mediated metabolic reprogramming and inhibits the growth and proliferation of tumor[348]. Tumor suppressor Ras association domain family 1A (RASSF1A) can also promote its stability and enhance the activation of Warburg effect by binding with HIF-1α[349]. Interestingly, HIF-1α can also activate its transcription through RASSF1A binding. RASSF1A−HIF-1α forms a feedforward loop to drive aerobic glycolysis[349].

Glucose metabolism can eliminate free radicals in mitochondria through pyruvate, which has a certain resistance to necrosis and apoptosis of cancer cells in hypoxic environment[350]. Necrosis is regulated by the formation and phosphorylation of receptor interacting protein kinase, receptor interacting protein 1−receptor interacting protein three complex. It can enhance the resistance of cancer cells to receptor interacting protein dependent necrosis by participating in the Warburg effect and regulating the aerobic glycolysis pathway[351]. High dimodulin expression, as a key factor in the formation of the three-dimensional structure of tumor cells, not only promotes increased glucose utilization by cancer cells but also accelerates the aerobic glycolysis process. It promotes the occurrence and development of cancer through the activation of the Warburg effect[352]. In some specific types of cancer, such as colorectal cancer, cancer cells do not decompose glucose into pyruvate and enter the tricarboxylic acid cycle to supply energy as normal cells do, but take glucose for metabolic synthesis through a higher rate of aerobic glycolysis. It is considered to provide tumor cells with an evolutionary advantage and provide more biosynthetic substances for the growth and reproduction of tumor cells[353]. Colon cancer-1 (MACC1) was first discovered in colon cancer. Its upstream and downstream constitute a delicate regulatory environment supporting its carcinogenic effect[354]. MACC1 promotes Warburg effect by regulating PI3K/protein kinase B (Akt) signal pathway, thus accelerating the occurrence and development of colorectal cancer[355]. PTEN, as a tumor suppressor, is often mutated or deleted in a variety of cancer types[356−359]. Its overexpression also depends on PI3K to block metabolic transformation and inhibit the occurrence of aerobic glycolysis[360]. The effector mTOR downstream of AKT can also provide ATP and other nutritional requirements for cancer cells by promoting central carbon metabolism[361]. The overexpression of glycolytic enzyme GPI in many human cancers is associated with poor prognosis[362]. The metabolism of cancer cells is characterized by extensive aerobic glycolysis dependence, but the single drug use of aerobic glycolysis inhibitors may promote the metabolic reprogramming of cancer cells mediated by mTORC1/S6K1 to avoid fragile aerobic glycolysis dependence. Combining the inhibition of mTORC1 on the basis of inhibition of aerobic glycolysis may be a potential strategy to deal with the phenomenon of aerobic glycolysis resistance. A study found that the silencing of GPI and the combination of mTORC1 inhibitor Everoliumus can reduce the growth of xenograft tumors by blocking metabolic reprogramming[361]. It is noteworthy that the high basic level of phosphorylated p70 S6 kinase and ribosomal protein S6 (P-S6) is negatively correlated with the sensitivity of cancer cells to aerobic glycolysis inhibitor 2-deoxyglucose (2DG), which can be used as a predictor of the response of cancer cells to aerobic glycolysis inhibition[361]. As a metabolic sensor, AMPK is usually involved in the negative regulation of mTOR to maintain cell energy homeostasis[363,364]. Its deletion accelerated the occurrence of HIF-1-induced aerobic glycolysis under normoxic stable conditions, and promoted the progress of Myc-mediated lymphoma[365].

Interestingly, there is no enhancement of Warburg effect in circulating chronic lymphoblastic leukemia (CLL) cells[366,367], but after contact with the matrix microenvironment, it promotes the metabolism of CLL into aerobic glycolysis through Notch−c-Myc signal transduction[368], which contributes to the drug resistance of cancer cells[369]. Tumor suppressor follicular protein (FLCN) can also interact with AMPK and inhibit its activation of HIF[370,371], which hinders AMPK-mediated Warburg effect and ultimately inhibits the occurrence and development of cancer[372]. PKM2 expressed only in normal embryonic stage will be re-expressed in most cancer cells[146]. PKM2 expression is necessary for Warburg effect. PKM2 K305 acetylation will reduce its enzyme activity and promote its degradation through HSC70 chaperone-mediated autophagy (CMA), thus reversing the aerobic glycolysis process[373]. The double specific phosphatase Cdc25A, which is up-regulated in various types of cancer[374], can mediate the dephosphorylation of PKM25 to promote aerobic glycolysis and tumorigenesis[375]. Protein arginine *N*-methyltransferase 6 (PRMT6) promotes PKM2 nuclear relocation and inhibits ERK/PKM2 axis-driven aerobic glycolysis by methylation of CRAF at arginine 100 and interference of RAS/RAF signal transduction to ERK[376]. The deletion of PKM2-mediated tumorigenicity and sorafenib resistance in HCC mouse models and clinical samples, which was reversed by the aerobic glycolysis inhibitor 2DG[376], Suggesting that targeting the PRMT6−ERK−PKM2 regulatory axis could be a potential strategy for treating sorafenib resistance events in HCC. Under the conditions of up-regulation of K-Ras

G12V and B-Raf V600E expression and activation of EGFR, ERK can also drive phosphorylation of PGK1 S203 and lead to mitochondrial translocation, and induce PGK1 to act as a protein kinase in TCA cycle to promote Warburg effect and induce cancer[377]. Another study found that when the downstream signal molecule of Kras/ERK pathway, guanosine triphosphatase ADP ribosylation factor 6 (ARF6) was knocked down, Warburg effect could be inhibited and pancreatic cancer cell proliferation could be reduced[378], which could be used as a new prognostic marker for pancreatic cancer. A study has found that HCC is often accompanied by epigenetic changes, in which the expression of lymphatic specific helicase (HELLS) is significantly up-regulated in HCC and induces aerobic glycolysis[379]. The depletion of HELLS will reverse the Warburg effect, ultimately inhibiting the growth and metastasis of HCC *in vivo* and *in vitro*[379]. In addition, a new epigenetic regulatory modification method, *N*-methyladenosine (mA) modification of RNA, has also been found to have anticancer efficacy in CRC patients by affecting aerobic glycolysis. METTL3, as a clinical oncogene of CRC, interacts with HK2 and GLUT1 through the mA-IGF2BP2/3 dependent mechanism and stabilizes their expression, ultimately activating the glycolytic pathway. Targeting METTL3 and its mA modification may be a potential strategy for treating CRC[380]. Interestingly, the expression level of lncRNA LINRIS is negatively correlated with OS in CRC patients. LINRIS blocks the K139 ubiquitination of the mA "reader" IGF2BP2, preventing its degradation. Knocking down LINRIS can correspondingly hinder the downstream effect of IGF2BP2, cause metabolic changes in CRC cells, and inhibit MYC-mediated aerobic glycolysis process[381].

As a key transcription factor of aerobic glycolysis, the proto-oncogene c-Myc is directly involved in regulating the expression of genes related to glucose metabolism[382,383]. Soft tissue sarcoma is divided into more than 70 subtypes due to its strong heterogeneity[384,385], the targeted treatment strategy is not optimistic, and the response rate to cytotoxic chemotherapy is also low[386]. Some researchers found that fructose-1,6-diphosphatase 2 (FBP2) is missing in most STS subtypes. Forcing FBP2 expression can simultaneously inhibit aerobic glycolysis and c-Myc-mediated TFAM expression, hinder mitochondrial biogenesis and respiration, thus inhibiting the proliferation of STS[387]. In addition, the recovery of FBP1 expression can also treat breast cancer and ccRCC by inhibiting Warburg effect[388,389]. The E3 ubiquitin ligase RING finger protein 6 (RNF6) overexpressed in pancreatic cancer (PC) can promote the degradation of MAD1 through the ubiquitin−proteasome pathway, upregulate the expression of c-Myc, and promote the Warburg effect in PC[390]. It is suggested that RNF6 may be a new biomarker in PC. SIRT6, a member of NAD-dependent protein deacetylase family, can also regulate ribosomal metabolism by inhibiting MYC transcription activity[391−393], and its expression level is negatively correlated with poor prognosis[393]. It is suggested that SIRT6 may be a molecular switch regulating Warburg effect. In addition, *p53*, the most common mutant gene in cancer, can also regulate the balance between respiratory and glycolytic pathways, while wild-type p53 in cancer often destroys the synthesis of cytochrome *c* oxidase 2 (*SCO2*) gene downstream of Warburg effect[394]. The deletion of p53 increased the expression of SCO2 and promoted the metabolic transformation to Warburg effect[394]. It provides a research direction for revealing the molecular mechanism of p53 regulation of the regulating Warburg effect in cancer. CDK8 is an oncogene that promotes the proliferation of cancer cells in various types of cancer[395−399]. Its activity is necessary for the aerobic glycolysis cascade reaction. The deletion of CDK8 can make colorectal cancer cells sensitive to aerobic glycolysis inhibitors[400]. TNBC is the most heterogeneous breast cancer, often accompanied by poor clinical prognosis[401]. Isocitrate dehydrogenase 2 (IDH2) is overexpressed in TNBC and induces aerobic glycolysis through serine biosynthesis pathway in the presence of phosphoglycerate dehydrogenase and phosphate aminotransferase[402]. This study found that phosphoglycerate dehydrogenase and phosphate aminotransferase as IDH2 synthetic dosage lethal partners may be potential targets for the treatment of TNBC in the future (Table 4) (Fig. 4).

The maintenance of cellular metabolic homeostasis relies on a multi-level and multi-dimensional three-dimensional regulatory network between the body and cells, as well as within cells, known as the cellular metabolic signaling network. This network is very complex, including various growth factor signaling pathways (such as EGFR), tumor suppressors (such as p53), oncogenic factors (such as mTOR), HIF-1α, c-MYC, and AMPK. The metabolic pathways within cells are interdependent and mutually constrained, maintaining the steady state of cellular metabolism.

4.5. *Mutations, tumor microenvironment and others*

Mutations are significant triggers for tumor occurrence and development, as well as a key factors contributing to the disordered the Warburg effect. Wild-type IDH1/2 can promote aerobic glycolysis to enhance the survival and proliferation of cancer cells, while in IDH mutant (IDH (mt)) tumor cells, the expression of certain essential glycolytic genes is down-regulated[403], and the key glycolytic gene *LDHA* showed low expression and hypermethylation in IDH (mt) GBM[404,405]. The tumor suppressor gene wild-type p53 suppresses the Warburg effect in tumors by regulating the energy metabolism related genes SCO2, TIGAR, GLS2 and Parkin[406−409]. As the most common mutated gene, wild-type p53 became mutp53 after mutation[410]. The latter induced Warburg effect by promoting GLUT1 translocation to the plasma membrane after the activation of RhoA/ROCK pathway[411]. The inhibition of RhoA/ROCK/GLUT1 signal pathway can reverse the Warburg effect and inhibit the occurrence of cancer[411]. In addition, splicing factor 3b subunit 1 (SF3B1) plays an important role in the correct splicing of mRNA[412−415]. However, hot spot gene mutations of *SF3B1* often occur in different types of human cancer[416−420]. SF3B1 K700E mutation causes abnormal splicing of PPP2R5A in PDAC, and promotes the proliferation of PDAC cells through the activation of aerobic glycolysis regulator c-Myc through post-translation regulation[421]. SF3B1 knockout or PP2A activator FTY-720 can significantly inhibit the SF3B1 K700E mutant PDAC model *in vitro* and *in vivo*[421].

Importantly, many factors in the microenvironment affect the metabolism of tumor cells. Hypoxia is the main factor that affects the metabolic state of tumor cells. Hypoxia can induce the stabilization of HIFs, improve glucose uptake by up-regulating GLUT1 and GLUT3, up-regulate the key enzymes of aerobic glycolysis, accelerate the aerobic glycolysis process, up-regulate pyruvate dehydrogenase kinase, inhibit pyruvate dehydrogenase activity and inhibit OXPHOS, make cells more dependent on aerobic glycolysis pathway to produce ATP, and finally complete the transformation from OXPHOS to aerobic hydrolysis[422]. Tumor cells that are over-dependent on aerobic glycolysis metabolism pathway, when exposed to areas with perfect blood supply and sufficient oxygen, the energy metabolism mode changes to

Table 4 Oncogenic protein/Tumor suppressor.

Name	Classification	Effect on Warburg effect	Regulatory mechanism	Cancer type	Ref.
p38γ MAPK	Oncogenic protein	+	Up-regulation of p38γ increases the expression of PFKFB3 and GLUT2 to enhance aerobic glycolysis	Pancreatic ductal adenocarcinomas (PDAC)	89
CUEDC2 (CUE domain-containing protein 2)	Oncogenic protein	+	CUEDC2 promotes the expression of GLUT3 and LDHA	Hepatocellular carcinoma	93
TAp73	Oncogenic protein	+	Ap73 increases the expression of phosphofructokinase-1, liver type (PFKL) to promote aerobic glycolysis	Osteosarcoma; colon cancer; lung cancer	130
ERK2	Oncogenic protein	+	ERK2 binds and phosphorylates PKM2 at Ser 37 to promote its nuclear translocation, therefore up-regulate c-Myc expression	Glioblastoma	148
AKT	Oncogenic protein	+	The PI3K/AKT pathway activates the transport of glucose, decreases glycogen synthesis *via* regulation of HK and PFK.	Hepatocellular carcinoma	
TGF-β1	Oncogenic protein	+	TGF-β1 activates Smad, p38 MAPK, PI3K/AKT pathways as well as HIF-1α up-regulation.		
Aurora-A	Oncogenic protein	+	Aurora-A phosphorylates LDHB at serine 162 and increases LDHB activity to contribute to the Warburg effect	Colorectal adenocarcinoma	155
CD147	Oncogenic protein	+	CD147 promotes the expression of MCT1 and increases p53 degradation to facilitate the Warburg effect.	Hepatic carcinoma	166
Calcium binding protein 39-like (CAB39L)	Tumor-suppressor	−	CAB39L interacts with LKB1−STRAD complex and then activation of the LKB1-AMPKα/β-PGC1α pathway to enhance the mitochondrial OXPHOS	Gastric cancer	206
LKB-1	Tumor-suppressor	−	LKB1 activates AMPK-PGC1α pathway to inhibit aerobic glycolysis	Gastric cancer	206
METTL3	Oncogenic protein	+	METTL3 installs the m^6A modification and enhances ABHD11-AS1 transcript stability to increase its expression thus to enhance the Warburg effect	Non-small-cell lung cancer	213
IRF6	Tumor-suppressor	−	IRF6 inhibited the transcription of PKM2 and GLUT1, thereby impairing aerobic glycolysis	Glioma	222
Stat3	Tumor-suppressor	−	Stat3 activates miR-23a to regulate PGC-1α and G6PC thus to decrease the glucose production	Hepatocellular carcinoma	267
mTOR complex 2	Oncogenic protein	+	mTORC2 up-regulates the cellular level c-Myc to control the aerobic glycolysis through mtorc2-HDAC−FOXO pathway	Glioblastoma	275
Lin28 A/B	Oncogenic protein	+	Lin28 A/B increases PDK1 protein expression and PI3K−AKT activation to promote aerobic glycolysis	Hepatoma	282
SIAH2	Oncogenic protein	+	SIAH2 degrades NRF1 (nuclear respiratory factor 1) *via* ubiquitination it on lysine 230 thus to inhibit the expression of pyruvate dehydrogenase beta to enhance the Warburg effect	Breast cancer	333
Rho-related BTB domain-containing protein 3 (RHOBTB3)	Tumor-suppressor	−	RHOBTB3 interacts with the hydroxylase PHD2 to promote HIFα hydroxylation, ubiquitination and degradation to repress the Warburg effect	Renal carcinoma	346
Metastasis associated with the colon cancer 1 (MACC1)	Oncogenic protein	+	MACC1 promotes the Warburg effect *via* PI3K/AKT signaling pathway	Gastric cancer	355
PTEN	Tumor-suppressor	−	PTEN inhibits aerobic glycolysis *via* PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase isoform 3) inhibition and PI3K/mtor/PKM2 suppression		360

(*continued on next page*)

Table 4 (*continued*)

Name	Classification	Effect on Warburg effect	Regulatory mechanism	Cancer type	Ref.
mTOR complex 1	Oncogenic protein	+	mTORC1 directs the increased glucose flux back to aerobic glycolysis through the pentose phosphate pathway	Ovarian cancer	361
AMPK	Tumor-suppressor	−	AMPKα suppresses aerobic glycolysis through HIF-1α inhibition	Lymphomas	365
Notch	Oncogenic protein	+	Notch promotes the Warburg effect *via* c-Myc activation	Chronic lymphocytic leukemia (CLL)	369
Folliculin (FLCN)	Tumor-suppressor	−	FLCN is an AMPK binding partner and inhibits HIF-dependent aerobic glycolysis	Endometrial adenocarcinoma	372
HSC70	Tumor-suppressor	−	PKM2 interacts with HSC70 and promotes its lysosomal-dependent degradation.	Cervical cancer	373
CDC25A	Oncogenic protein	+	CDC25A-mediated PKM2 dephosphorylation could up-regulation of the expression of the glycolytic genes	Glioblastoma	375
N-Methyltransferase 6 (PRMT6)	Tumor-suppressor	+	PRMT6 methylates CRAF to inhibit ERK-mediated PKM2 activation	Hepatocellular carcinoma	376
EGFR	Oncogenic protein	+	The activation of EGFR induces ERK-dependent phosphoglycerate kinase 1 S203 phosphorylation to promote its mitochondrial translocation, Mitochondrial PGK1 phosphorylate pyruvate dehydrogenase kinase 1 at T338 to inhibit the pyruvate dehydrogenase (PDH) complex to enhance the Warburg effect.	Glioma	377
ADP ribosylation factor 6 (ARF6)	Oncogenic protein	+	ARF6 maintains the activation of ERK/c-Myc axis to enhance the Warburg effect	Pancreatic cancer	378
Helicase, lymphoid-specific (HELLS)	Oncogenic protein	+	HELLS inhibits multiple tumor suppressor genes expression to facilitate the Warburg effect	Hepatocellular carcinoma	379
Gluconeogenic isozyme fructose-1,6-bisphosphatase 2 (FBP2)	Tumor-suppressor	−	Nuclear FBP2 represses c-Myc-dependent TFAM expression to block the Warburg effect	Sarcoma	387
Fructose-1,6-bisphosphatase 1 (FBP1)	Tumor-suppressor	−	FBP1 interacts with the HIF inhibitory domain to inhibit nuclear HIF function	Renal carcinoma	389
E3 ubiquitin ligase RING-finger protein 6 (RNF6)	Oncogenic protein	+	RNF6 enhances c-Myc-mediated aerobic glycolysis.	Pancreatic cancer	390
SIRT6	Tumor-suppressor	−	SIRT6 suppresses aerobic glycolysis through MYC inhibition	Pancreatic and colorectal cancers	393
SIRT3	Tumor-suppressor	−	SIRT3 inhibits the Warburg effect through PHD regulated HIF-1α destabilization	Breast cancers	348
Ras association domain family 1A (RASSF1A)	Oncogenic protein	+	RASSF1A regulates HIF-1α stability to increase HIF-1α mediated the transcription of genes associated with aerobic glycolysis	Cervical cancer	349
Synthesis of cytochrome *c* oxidase 2 (SCO2)	Tumor-suppressor	−	SCO2 regulates the cytochrome *c* oxidase (COX) complex to inhibit the Warburg effect	Human colon cancer	394
CDK8	Oncogenic protein	+	CDK8 promotes the expression of multiple glycolytic genes	Colorectal carcinoma	400
Isocitrate dehydrogenase 2 (IDH2)	Oncogenic protein	+	IDH2 regulates the serine biosynthesis pathway to affect the TCA cycle and aerobic glycolysis	Triple-negative breast cancer (TNBC)	402

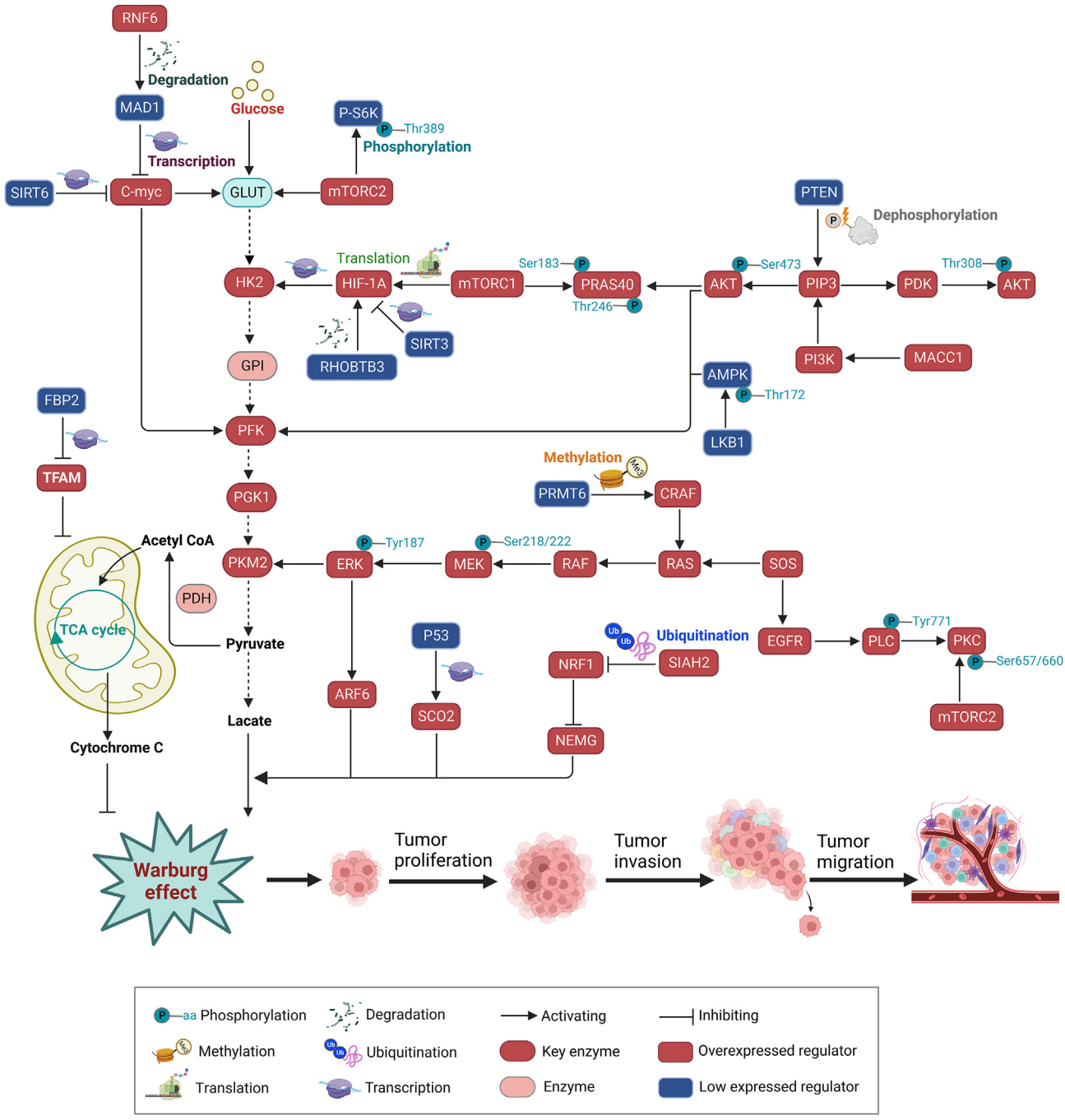


Figure 4 Protein–protein interactions regulating the Warburg effect. Mechanisms of protein–protein interactions include phosphorylation, methylation and ubiquitination. One protein can also promote the transcription or translation of another protein to increase the expression of the interacting partner.

OXPHOS, and the ability of metastasis and invasion is enhanced. The change of nutritional components in tumor microenvironment will also affect the metabolic mode of tumor cells. HeLa cells are mainly dependent on aerobic glycolysis pathway in the presence of glucose. However, when the culture environment contains only galactose, HeLa cells decompose galactose through OXPHOS to maintain their own proliferation[423]. The rapid proliferation of tumor cells needs to consume a lot of glucose and oxygen, resulting in a relative lack of nutrition and the formation of local hypoxia microenvironment. Hypoxia, low pH value, nutrient deficiency and other physical and chemical conditions are conducive to the proliferation and metastasis of tumor cells[424]. These characteristic physical and chemical conditions are involved in regulating tumor energy metabolism and reprogramming, and are also indispensable for tumor cell survival[425]. The rate of cell growth and catabolism is regulated by various levels of cell regulatory systems, including gene expression, post-transcriptional regulation, translation, and post-translational modification, which ultimately affect metabolic flux[426]. Metabolic transformation is usually associated with oxygen restriction,

genetic disturbance and overflow metabolism[427]. For example, fructose 1,6-bisphosphate (FBP), a glycolytic metabolite, interferes with respiratory activity and regulates metabolic flux through transcription factors[426]. The inhibition of Warburg effect of cancer cells will lead to the crisis of their cell bioenergy and further induce the death of cancer cells[428].

More and more evidence shows that tumor cells can regulate the expression level of substrate proteins through ubiquitination modification, thereby affecting the activation or inhibition of proteins on Warburg effect. Ubiquitination is a process of protein post-translational modification, characterized by the covalent linkage between ubiquitin molecules and protein substrates. Ubiquitination modification process is reversible and dynamic. It mediates the occurrence and development of tumors by participating in regulating gene transcription, inflammatory response, DNA damage repair and other biological processes[429]. The regulatory mechanism of ubiquitination/de ubiquitination on Warburg effect in tumor cells is complex, and its mechanism is an important regulatory point for normal cells and tumor cells[430]. In recent years, with the deepening of research on autophagy, the close relationship between autophagy and "Warburg effect" has garnered significant interest from researchers[431]. Autophagy and tumor energy metabolism are considered to be highly related to clinical practice and become the focus of cancer transformation research[432]. In tumor microenvironment, tumor cells and interstitial cells play an important role in tumor genesis and metastasis through the interaction of growth factors and various cytokines. Tumor cells "hijack" peripheral interstitial cells or cancer-associated fibroblast (CAF), and use the high-energy metabolites produced by CAF to maintain the metabolic needs of tumor cells. The activation of oncogene and the large amount of reactive oxygen species secreted by tumor cells can induce CAF to produce oxidative stress, and then induce autophagy of CAF[433]. ROS can also destroy mitochondrial metabolic enzymes, thus inhibiting TCA cycle, causing damage to mitochondrial function, and increasing CAF aerobic glycolysis[434]. The high-energy metabolites such as lactic acid and ketone produced by CAF autophagy and the "Warburg effect", in turn, provide fuel and necessary "chemical building materials" for the mitochondrial biosynthesis and oxidative phosphorylation of tumor cells, resulting in an immortal vicious cycle of tumor cells. This process is called "epithelial mesenchymal metabolic coupling", also known as "reverse Warburg effect"[435–437]. In addition, autophagy can activate the aerobic glycolysis pathway to promote cell glucose metabolism and ultimately promote its proliferation and transformation to tumor during tumor development[437]. In addition, proinflammatory cytokines, tumor necrosis factor-α and IL-17 will also stimulate and strengthen the aerobic glycolysis of cancer cells and inhibit the oxidative phosphorylation of mitochondria, providing more powerful energy support for the development and metastasis of cancer[438] (Table 5).

Table 5 Mutations, tumor microenvironment and others.

Name	Classification	Regulation on Warburg effect	Regulatory mechanism	Cancer type	Ref.
LPS			LPS activates TLR4 to enhance aerobic glycolysis *via* uPFK2 activation		
KRAS4A	Oncogenic protein (mutation)	+	KRAS4A targets HKI to initiate the Warburg effect	Pancreatic cancer	104
Glucose		−	High glucose promotes the acetylation of PKM2 at K305 *via* the acetyltransferase PCAF and decreases PKM2 enzyme activity and promotes its lysosomal-dependent degradation.	Cervical cancer	373
K-Ras G12V	Oncogenic protein (mutation)	+	The activation of K-Ras G12V and B-Raf V600E induce ERK-dependent activation of the warburg effect.	Glioma	377
B-Raf V600E	Oncogenic protein (mutation)	+			
Mutant isocitrate dehydrogenase 1 (IDH1) Mutant isocitrate dehydrogenase 2 (IDH2)	Tumor suppressor (mutation)	−	IDH(mt) in gliomas downregulated the expression of LDHA and many HIF1α-responsive genes to limit the aerobic glycolysis.	Gliomas	403
Mutant p53	Oncogenic protein (mutation)	+	Mutp53 promotes the Warburg effect through RhoA/ROCK/GLUT1 signalling	Breast cancer	411
SF3B1 K700E	Oncogenic protein (mutation)	+	MutSF3B1 stimulates the aerobic glycolysis through PP2A-c-Myc activation	Pancreatic ductal adenocarcinoma	421
Fructose 1,6-bisphosphate (FBP)	Intracellular metabolite		FBP senses the flux of the upper aerobic glycolysis, and regulates the lower glycolytic flux by the allosteric activation of pyruvate kinase		426

5. Targeting Warburg effect as cancer strategies

5.1. *Classic strategies*

5.1.1. *Synthetic small molecule drugs*

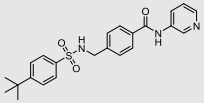
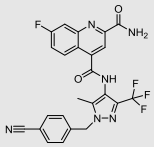
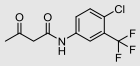
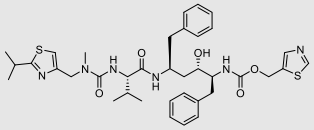
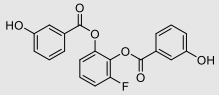
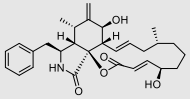
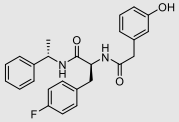
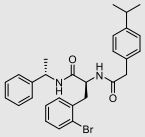
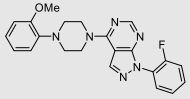
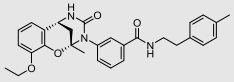
5.1.1.1. GLUT inhibitors. The proliferation of tumor cells may depend on specific GLUTs or particular subtypes of key glycolytic enzymes. It may provide new clues for the treatment of cancer by

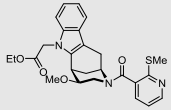
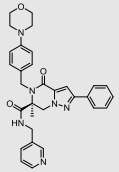
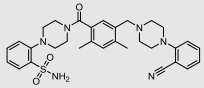
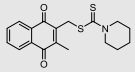
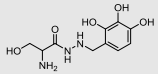
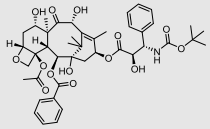
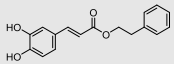
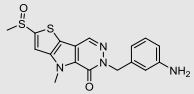
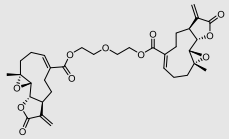
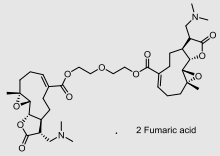
taking this as the target of action, using specific drug targeted therapy, regulating the glucose metabolism of tumor cells, and inhibiting the growth of cancer cells (Table 6) (Fig. 5A). It is noteworthy that high GLUT-1 expression is associated with high invasion and tumor incidence of various types of cancer[439–441]. A study reported the pharmacological identification results of a series of compounds, in which STF-31 inhibits glucose uptake mediated by GLUT1, selectively inhibits the proliferation and growth of RCCs, and has no adverse reactions[82]. In addition, researchers have designed and synthesized a more selective GLUT1 inhibitor BAY-876. *In vitro* PK data shows good metabolic stability in liver cells, while *in vivo* PK data shows high oral bioavailability and a longer end half-life, suggesting that BAY-876 may be a highly potential selective GLUT1 inhibitor in tumor treatment[442]. As an effective glucose uptake inhibitor, fasentin can selectively target GLUT-1/GLUT-4 transporter and has anti-angiogenic activity[443,444]. Upregulation of GLUT-4 expression in low-glucose microenvironment can significantly promote the invasion and metastasis of tumor cells[445–449]. The combination of GLUT4 inhibitor Ritonavir and HNF4A agonist Benfluorex can inhibit glucose uptake and proliferation of HCC cells by mediating AMPK2/HNF4A/BORIS/GLUT4 signal pathway[450]. In addition, high GLUT-1 expression is associated with chemoresistance of various types of cancer[451,452]. After being treated with GLUT-1 inhibitor WZB117, imatinib-resistant cells exert synergistic growth inhibition by reducing AKT phosphorylation and Bcl-2 expression, overcoming the imatinib-resistance of gastrointestinal stromal tumors[453]. Cytochalasin B, as a pan inhibitor of GLUT, can hinder the transport of glucose and glucosamine in liver cancer cells by inhibiting GLUT-1−4 targets[454–456]. The structure of single transporter human glucose transporter 1 (hGLUT1) has been elucidated, and the Phe amide derived inhibitors GLUT-i1 and GLUT-i2 bind to the specific glucose substrate binding site of hGLUT1 and inhibit its glucose transport function[457]. Their co-complex structure provides important structural insights for designing more selective hGLUT1 inhibitors. A series of 1-pyrazolo [3,4-*d*] pyrimidine derivatives also showed good binding to GLUTs, with compound **3** showing significant inhibitory effects on GLUT1 and good selectivity for GLUT2, while exhibiting good metabolic stability and pharmacokinetic characteristics[458]. Some new glucose uptake inhibitors chromopynone-1 and glupin can selectively target GLUT1/3 to regulate cancer metabolism and ultimately inhibit the growth of various types of tumor cells[459,460]. As a glucose uptake inhibitor, glutor can also inhibit aerobic glycolysis flux by targeting GLUT1/2/3, and ultimately play a role in inhibiting growth in many cancer cell lines[461]. Interestingly, NV-5440 can regulate cell metabolism by simultaneously targeting mTORC1 and GLUT1, effectively inhibit glucose uptake, and inhibit the proliferation of breast cancer cells[462]. Its pharmacokinetics *in vivo* shows that NV-5440 has good stability *in vivo*[462]. This new dual target inhibitor provides a promising research direction for future Warburg effect inhibitor development strategies.

5.1.1.2. PKM2 inhibitors and agonists. PKM2 is one of the key enzymes of aerobic glycolysis. In recent years, many studies have found that its expression is enhanced in tumor tissue. In lung adenocarcinoma cells, PKM2 knockout significantly inhibited cell proliferation, glucose absorption, ATP and fatty acid synthesis, and enhanced mitochondrial respiratory capacity. More importantly, PKM2 knockout inhibits matrix metalloprotein 2 and VEGF, indicating that reducing PKM2 expression can inhibit tumor growth, metastasis and invasion[431]. It is suggested that PKM2 inhibitors may exert anticancer effects by inhibiting aerobic glycolysis, and the research and development of PKM2 inhibitors are promising anticancer strategies in the future. In various types of cancer, the use of chemotherapy drug cisplatin often leads to resistance, and PKM2 inhibitor Shikonin can reverse cisplatin resistance by inducing necrotic apoptosis, thereby improving the efficacy of cisplatin in treating cancer[463–465]. A novel naphthoquinone derivative C3k exhibits better inhibitory activity against PKM2 targets than Shikonin, and C3k exhibits significant anti proliferative activity in multiple types of tumor cell lines with higher PKM2 levels[466–468]. Interestingly, benserazide, a dopamine decarboxylase inhibitor for Parkinson's disease, can also specifically bind and block PKM2 enzyme activity, inhibit aerobic glycolysis, and thus inhibit the growth of melanoma[469]. The combination therapy of docetaxel and caffeic acid phenethyl ester can also inhibit the expression of PKM2, thereby impeding the metabolic process of tumor cells, inducing cell apoptosis, and ultimately inhibiting the proliferation of prostate cancer cells[470]. These findings provide more ideas for the combined use of drugs to treat tumors. It is worth noting that PKM2 expression appears to be crucial for tumor formation[471], but studies have also shown that using PKM2 expression can replace PKM1's shRNA, thereby reducing lactate production and increasing oxygen consumption, reversing the Warburg effect[147]. There is a hypothesis that increasing PKM2 activity to PKM1 level may also have anti-proliferative effects. ML-265, as a PKM2 activator, reduces PGAM1 phosphorylation by activating PKM2 *in vitro* and *in vivo* models of lung cancer, ultimately inhibiting tumor growth[472]. A series of parthenolide dimers have also been found to have PKM2 activation activity. Among them, compounds **5** and **16** inhibit STAT3 signaling pathway, ultimately inhibit GBM cell proliferation and metastasis, and inhibit tumor growth while promoting the formation of PKM2 tetramer without affecting the expression of total PKM2[473].

5.1.1.3. HK2 inhibitors. 2-DG and 3-bromopyruvate are classic inhibitors targeting tumor glycolytic enzyme HK2[474,475]. After using fasentin, 2-DG and 3-bromopyruvate in cancer cells treated with mitochondrial respiratory regulators, glucose uptake and aerobic glycolysis were inhibited, but the survival rate of irradiated cells was not improved[476]. It is suggested that enhanced aerobic glycolysis is the reason for inhibiting mitochondrial respiratory related radioresistance. Interestingly, 3-bromopyruvate, the second-generation aerobic glycolysis inhibitor, has a stronger anticancer effect. Some studies have found that 3-bromopyruvate can eliminate tumor tissue in all rat models of advanced liver cancer without recurrence and adverse reactions[477]. Cisplatin is often resistant to chemotherapy drugs because of ATP-dependent multidrug resistance phenotyp. The addition of 3-bromopyruvate, a multidrug resistance reversal regulator[478], reverses the drug resistance of cisplatin by causing ATP depletion, which has stronger synergistic anti-cancer effect than the use of cisplatin alone[479]. Drug repositioning research not only greatly reduces the development cycle of new drugs, but also reduces economic costs, and is increasingly receiving attention from the pharmaceutical industry[480]. Azole Antifungal, ketoconazole and posaconazole, were found to be able

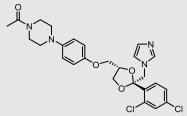
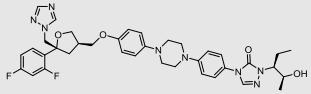
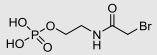
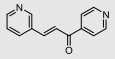
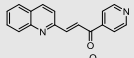
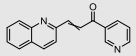
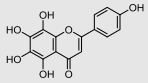
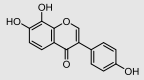
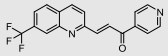
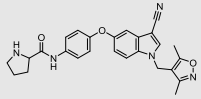
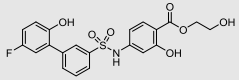
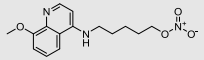
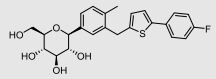
Table 6 Synthetic small molecule drugs.

Name in the literature	Chemical structure	Mechanism	Cancer cell line (activity)	Ref.
STF-31		Inhibit glucose uptake mediated by GLUT1	GLUT1: IC_{50} = 1 μmol/L; RCC4	82
BAY-876		Inhibit GLUT1	GLUT1: IC_{50} = 2 nmol/L; SKOV-3; OVCAR-3	442
Fasentin		Inhibit GLUT1/4	GLUT4: IC_{50} = 68 μmol/L; PPC-1; DU145; U937	443
Ritonavir		Mediate AMPK2/HNF4A/BORIS/GLUT4 signal pathway	Huh-7; HCC-LM3; Hepg2; SMMC-7721; PLC/PRF/5	450
WZB117		Reduce AKT phosphorylation and Bcl-2 expression by inhibiting GLUT1	GLUT1: IC_{50} = 10 μmol/L A549; MCF7; GIST-T1; GIST-T1/IM-R	453
Cytochalasin B		Hinder the transport of glucose and glucosamine by inhibiting GLUT 1−4 targets	B16F10: 0.4 μmol/L	454, 455
GLUT-i1		Inhibit hGLUT1	Glut1: IC_{50} = 0.267 ± 0.133 μmol/L; Glut2: IC_{50} = 56 ± 13.6 μmol/L; Glut3: IC_{50} = 5.2 ± 1.1 μmol/L; Glut4: IC_{50} = 0.195 ± 0.066 μmol/L	457
GLUT-i2		Inhibit hGLUT1	Glut1: IC_{50} = 0.140 ± 0.072 μmol/L; Glut2: IC_{50} > 30 μmol/L; Glut3: IC_{50} = 7.7 ± 1.35 μmol/L; Glut4: IC_{50} = 0.090 ± 0.08 μmol/L	457
Compound **3**		Inhibit GLUT1/2	Glut1: IC_{50} = 7 nmol/L; Glut2: IC_{50} = 1.1 μmol/L; Glut3: IC_{50} = 40 nmol/L	458
Chromopynone-1		Inhibit GLUT1/3	IC_{50} = 412 ± 120 nmol/L; UM-UC-3: GI_{50} = 4 nmol/L; MIA PaCa-2: GI_{50} = 4 nmol/L	459

Glupin		Inhibit GLUT1/3	DLD-1: IC_{50} = 59.6 ± 8.4 nmol/L; DLD-1 $GLUT1^{-/-}$: IC_{50} = 11.4 ± 1.6 nmol/L; UM-UC-3: IC_{50} = 32 nmol/L; MIA PaCa-2: IC_{50} = 61 nmol/L; WSU-NHL: IC_{50} = 62 nmol/L; SU-DHL-6: IC_{50} = 92 nmol/L; SK-N-SH: IC_{50} = 84 nmol/L	460
Glutor		Inhibit GLUT1/2/3	IC_{50} = 19 ± 2 nmol/L; MIA PaCa2: GI_{50} = 0.6 μmol/L; HCT116: GI_{50} = 3.8 μmol/L	461
NV-5440		Inhibit GLUT1 and mTORC1	$pS6K1^{T389}$: IC_{50} = 70 nmol/L; MCF7: IC_{50} = 36 nmol/L	462
C3k		Inhibit PKM2	HCT116: IC_{50} = 0.18 μmol/L; Hela: IC_{50} = 0.29 μmol/L	466
Benserazide		Inhibit PKM2	10 μmol/L; SK-MEL-5; SK-MEL-28	469
Docetaxel		Inhibit PKM2	PC/DX25: IC_{50} = 316.4 nmol/L	470
Caffeic acid phenethyl ester		Inhibit PKM2	PC/DX25: IC_{50} = 15.7 μmol/L	470
ML-265		Activate PKM2	H1299: IC_{50} = 92 nmol/L	472
Compound **5**		Activate PKM2	AC_{50} = 15 nmol/L; U87: IC_{50} = 3.03 ± 0.54 μmol/L; U118: IC_{50} = 1.80 ± 0.28 μmol/L; SF126: IC_{50} = 7.49 ± 0.45 μmol/L; SHG44: IC_{50} = 5.24 ± 2.46 μmol/L; U251: IC_{50} = 7.14 ± 0.06 μmol/L; C6: IC_{50} = 1.66 ± 0.01 μmol/L; 3T3: IC_{50} = 7.93 ± 3.21 μmol/L	473
Compound **16**		Activate PKM2	U118 tumor xenograft (50 mg/kg)	473
2-DG		Inhibit HK2	MCF-7	474, 476

(*continued on next page*)

Table 6 (*continued*)

Name in the literature	Chemical structure	Mechanism	Cancer cell line (activity)	Ref.
3-Bromopyruvic acid		Inhibit HK2	MCF-7: 80 μmol/L; MDA-MB-231: 160 μmol/L	475-477, 479
Ketoconazole		Inhibit HK2	U87: EC_{50} = 9.3 μmol/L; T89G EC_{50} = 9.5 μmol/L; U251: EC_{50} = 10.1 μmol/L; NHA: EC_{50} = 73 μmol/L	480
Posaconazole		Inhibit HK2	U87: EC_{50} = 9.7 μmol/L; T89G EC_{50} = 10.2 μmol/L; U251: EC_{50} = 11.6 μmol/L; NHA: EC_{50} = 80.3 μmol/L	480
N-Bromoacetyle thanolamine phosphate		Inhibit PFK2	K_i = 0.24 mmol/L; IC_{50} = 2.2 mmol/L	483
3PO		Inhibit PFKFB3	PFKFB3: IC_{50} = 22.9 μmol/L	484
PFK15		Inhibit PFKFB3	PFKFB3: IC_{50} = 207 nmol/L	490
PQP		Inhibit PFKFB3	T24; UM-UC-3	491
N4A		Inhibit PFKFB3	PFKFB3: Ki = 1.29 ± 0.26 μmol/L; IC_{50} = 2.97 ± 0.16 μmol/L; HeLa: GI_{50} = 14.2 ± 1.5 μmol/L	492
YN1		Inhibit PFKFB3	PFKFB3: K_i = 0.24 ± 0.03 μmol/L; IC_{50} = 0.67 ± 0.08 μmol/L; HeLa: GI_{50} = 8.2 ± 0.8 μmol/L	492
PFK158		Inhibit PFKFB3	PFKFB3: IC_{50} = 137 nmol/L; (NCT02044861)	493
compound **26**		Inhibit PFKFB3	PFKFB3: IC_{50} = 11 nmol/L; A549: GI_{50} = 281 nmol/L	495
KAN0438757		Inhibit PFKFB3	U2OS: 10 μmol/L	496
5MPN		Inhibit PFKFB4	H460	499
Metformin		Activate AMPK pathway	5 mmol/L; MDA-231; MCF-7; U2OS	500
2,3-Dihydro-2-(naphthalen-1-yl) quinazoline-4 (1*H*)-one (DHNQ)		Inhibit PI3K	Colo-205: IC_{50} = 0.25 ± 0.05 μmol/L; HCT-116: IC_{50} = 0.3 ± 0.1 μmol/L; Fr-2: IC_{50} = 4.2 ± 1.3 μmol/L;	502
Canagliflozin		Inhibit sodium-glucose cotransporter 2	10 μmol/L; Huh7; Hepg2	503

Romidepsin	Inhibit HDAC and reduce ATP production	U87: IC_{50} = 18.4 μmol/L	504
Panobinostat	Inhibit FAO and hinder the occurrence of OXPHOS	U87: IC_{50} = 0.78 μmol/L	504
Vorinostat	Inhibit FAO and hinder the occurrence of OXPHOS	U87: IC_{50} = 2.6 μmol/L	504
CX-4945	Downregulation of TAP73	AGS-1: 10 μmol/L	506
1,3-Benzodioxane derivative compound **10**	Inhibit LDHA	LDHA: IC_{50} = 47.20 μmol/L PANC-1: GI_{50} = 12.19 μmol/L	507

to target HK2 as tumor metabolism inhibitors to inhibit tumor metabolism, induce apoptosis, and finally play an effective anti-cancer role in GBM *in vivo* and *in vitro* models[481]. Unfortunately, most HK2 inhibitors are currently ineffective and have adverse reactions during clinical trials, making them unable to enter clinical practice[482].

5.1.1.4. PFK inhibitors. The first PFK2 inhibitor discovered is *N*-bromoacetylethanolamine phosphate, a non-competitive inhibition relative to ATP. Unfortunately, this reagent has no inhibitory activity on the phosphorylation of fructose 6-phosphate and is nonspecific for PFK2[483]. The researchers designed and synthesized the PFKFB3 inhibitor 3PO based on the homologous model of PFKFB3 isozyme[484], which has good anti-cancer activity in various types of tumor cells[485−487]. Due to the poor pharmacokinetic characteristics and low efficacy of 3PO[488], subsequent researchers have improved its efficacy by loading nanocarriers into multiple types of cells[489]. A new PFKFB3 inhibitor PFK15 with higher selectivity and stronger inhibitory activity was obtained by modifying the 3PO structure, which has better metabolic stability[490]. Another PFKFB3 inhibitor PQP exhibits an additive growth inhibitory effect when combined with LDHA inhibitors, although its inhibitory activity on cancer cell growth is weaker than PFK15[491]. In 2011, the crystal structure of PFKFB3 was confirmed, and two compounds N4A and YN1, which are more selective to PFKFB3, were virtual screened and identified to inhibit aerobic glycolysis in human cervical cancer and human breast cancer cells through targeted inhibition of PFKFB3, leading to cell death[492]. It is worth noting that a new PFKFB3 inhibitor PFK158 is currently undergoing a phase I clinical trial targeting patients with advanced solid malignant tumors, and a phase II clinical trial targeting leukemia patients is also being prepared[490]. PFK158 has also been found to play an anticancer role in gynecological cancer and mesophylioma[493,494]. Further weak screening for PFKFB3 kinase optimization revealed a more selective PFKFB3 inhibitor compound **26**[495]. PFKFB3 has been proven to be involved in homologous recombination repair of DNA double-strand breaks[496]. The new PFKFB3 inhibitor KAN0438757 inhibits the incorporation of deoxynucleotides during DNA repair by targeting PFKFB3, inhibits HR protein recruitment and reduces HR activity, and ultimately inhibits U2OS cell proliferation and growth[496]. A study proved that the level of PFKFB4 was negatively correlated with disease-free survival (DFS) and OS in tumor samples of breast cancer patients, which was associated with poor prognosis[497]. Knocking down PFKFB4 can inhibit tumor cell proliferation and metastasis, and overcome resistance to chemotherapy drugs[498]. Although research progress on PFKFB4 inhibitors has been slow, some studies have found that a compound 5MPN exerts anti-proliferative effects by inhibiting the PFKFB4 target in H460 adenocarcinoma cells[499]. The addition of 5MPN can also improve the sensitivity of carfilzomib to tumors[499].

5.1.1.5. The others. Metformin, as a hypoglycemic drug, has become an effective treatment for cancer. It can limit the function of mitochondria, and participate in activating AMPK pathway, reducing the use of glucose, thus inhibiting the Warburg effect[500,501]. Warburg effect has played a significant role in promoting the growth, proliferation, diffusion and metastasis of colorectal cancer cells, creating suitable environmental conditions for the proliferation and metastasis of cancer. 2,3-Dihydro-2-(naphthalen-1-yl) quinazoline-4 (1*H*)-one (DHNQ), as a new PI3K pathway inhibitor, down-regulates the metabolic flux of colorectal

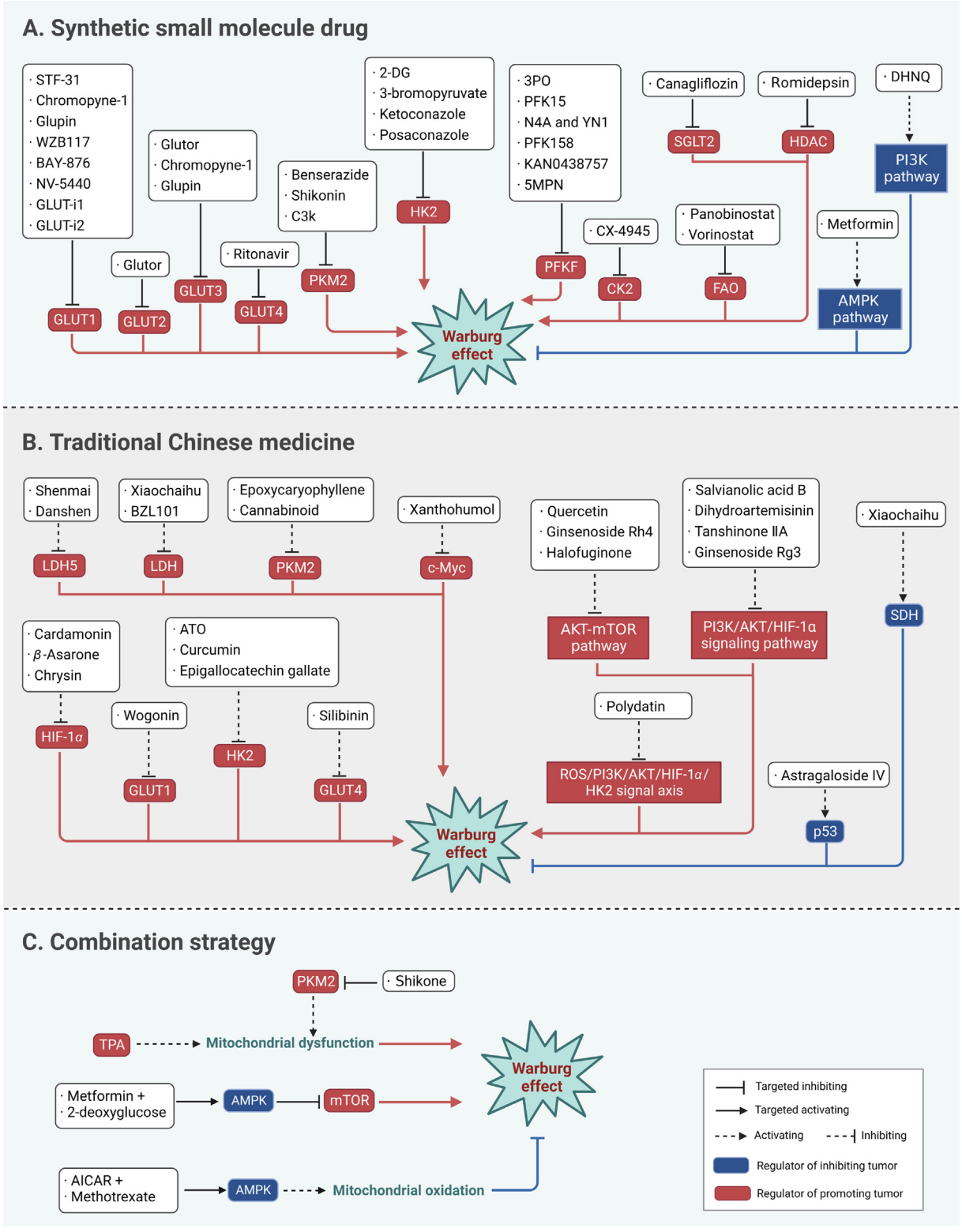
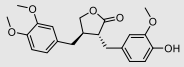
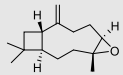
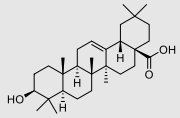
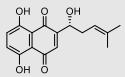
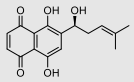
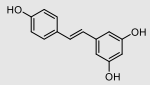
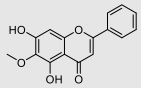
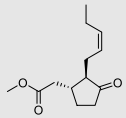
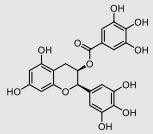
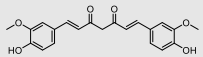


Figure 5 Multiple drugs targeting the Warburg effect for treating cancer. (A) Synthetic small molecule drug regulates the Warburg effect for inhibiting cancer progression. (B) Traditional Chinese Medicine targets the regulator of the Warburg effect for cancer treatment. (C) The combination strategy regulates the Warburg effect for interfering with cancer progression.

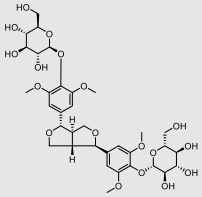
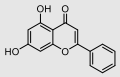
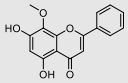
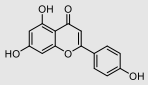
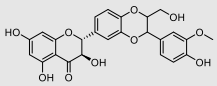
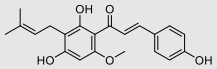
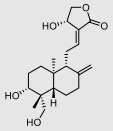
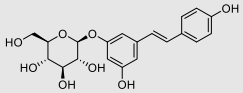
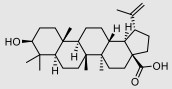
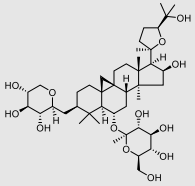
Table 7 Traditional Chinese medicine.

Name in the literature	Natural source	Chemical structure	Cancer cell line (activity)	Mechanism	Ref.
BZL101	*Scutellaria barbata* D. Don		Skbr3 (0.5 mg/mL); BT474 (0.5 mg/mL); U937 (IC_{50}~10 μg/mL)	Produce ROS, the excessive activation of PARP caused by DNA damage further inhibits cell aerobic glycolysis	512, 561
Arctigenin	*Arctium lappa* L.		A549 (IC_{50}~10 μmol/L, glucose-deprived, 8 h)	Inhibition of mitochondrial respiration reduced the cellular ATP content, resulting in the increase of ROS	515
Epoxycaryophyllene	*Annona squamosa* L. Bark.			Transform PKM2 into PKM1 by inhibiting aerobic glycolysis	517
Oleanolic acid	*Ligustrumlucidum*; *Araliachinensis*		PC-3; MCF-7	Regulate c-Myc-mediated PKM selective splicing by inhibiting the mtor pathway, resulting in a decrease in PKM2 and an increase in PKM1	518
Shikonin	*Lithospermum erythrorhizon* Sieb. Et Zucc.		MCF-7 (PKM2 IC_{50} = 0.8 μmol/L)	Selectively inhibit the activity of PKM2	30
Alkannin	*Lithospermum erythrorhizon* Sieb. Et Zucc.		MCF-7 (PKM2 IC_{50} = 0.9 μmol/L)	Selectively inhibit the activity of PKM2	30
Cannabinoids	*Cannabis sativa* L.		Panc1	Inhibit the Akt/c-myc pathway to reduce the expression and activity of PKM2	519
Arsenic trioxide	*Arsenolite/Arsenopyrite*; *Realgar*; *Orpiment*	As_2O_3	HEK293T; SGC7901; HK2 K_d = 12.3 nmol/L	Inhibit HK2	520
Resveratrol	*Reynoutria japonica* Houtt.; *Senna tora* (L.) Roxb.; *Morus alba* L.		HCC-LM3 (IC_{50} = 59.46 μmol/L); Bel-7402 (IC_{50} = 81.57 μmol/L); Huh-7 (IC_{50} = 111.37 μmol/L)	Inhibit aerobic glycolysis, ultimately promotes mitochondrial apoptosis, inhibits cell proliferation	521
Oroxylin A	*Scutellaria baicalensis* Georgi		MDA-MB-231; MCF-7	Induce dissociation of HK2 from the mitochondria and inhibits aerobic glycolysis by SIRT3-mediated deacetylation of cyclophilin D	524
Methyl-jasmonate	*Styrax grandiflorus* Griff.; *Tunisian rosemary* oil		CT-26	Promotion of HK2 dissociation from mitochondrial VDAC and the reduction of intracellular ATP level	525
Epigallocatechin gallate	Green tea		Tca8113 (40 μmol/L); Tscca (40 μmol/L)	Reduce the expression of HK2 protein by inhibiting AKT pathway	527
Curcumin	*Curcuma aromatica* Salisb.; *C. longa* L.; *C. zedoaria* (Berg.) Rosc.; *Acorus calamus* L.		HCT116 (IC_{50}≈40 μmol/L); HT29 (IC_{50}≈50 μmol/L)	Down-regulating the expression and activity of HK2	530

(*continued on next page*)

Table 7 (*continued*)

Name in the literature	Natural source	Chemical structure	Cancer cell line (activity)	Mechanism	Ref.
Quercetin	*Styphnolobium japonicum* (L.) Schott		SMMC-7721 (50 μmol/L); Bel-7402 (50 μmol/L)	Reduce HK2 and Akt-mTOR Pathway	531
Ginsenoside Rh4	*Ginseng*		KYSE 150 (IC_{50}≈60 μmol/L, 24 h)	Suppresses the expression of PD-L1 *via* targeting AKT	532
Cardamonin	*Alpinia katsumadai* Hayata		SKOV3 (20 μmol/L)	Inhibition of aerobic glycolysis by mTOR; Down-regulate HIF-1α-mediated cell metabolism	533, 539
Halofuginone	*Dichroa febrifuga* Lour.		SW480 (IC_{50} = 24.83 nmol/L); HCT116 (IC_{50} = 5.82 nmol/L); SW620 (IC_{50} = 40.76 nmol/L); HT29 (IC_{50} = 40.76 nmol/L); DLD-1 (IC_{50} = 60.89 nmol/L)	Suppression of Akt/mTORC1 signaling and glucose metabolism	533
Salvianolic acid B	*Salvia miltiorrhiza* Bunge		Cal27 (IC_{50} = 297 μmol/L); HN4 (IC_{50} = 201 μmol/L); Leuk1 (IC_{50} = 294 μmol/L)	PI3K/AKT/HIF-1α signal pathway	535
Dihydroartemisinin	*Artemisia annua* L.		Lncap (IC_{50}≈30 μmol/L)	PI3K/AKT/HIF-1α signal pathway	536
Tanshinone IIA	*Salvia miltiorrhiza* Bunge		Siha (IC_{50}≈0.75 mg/L, 48 h); Hela (IC_{50}≈2 mg/L, 48 h); C33a (IC_{50}≈4 mg/L, 48 h); CAL27 (IC_{50}≈2 μmol/L); SCC15 (IC_{50}≈5 μmol/L)	PI3K/AKT/HIF-1α signal pathway; Reducing AKT/c-Myc signal	537, 555
Ginsenoside Rg3	*Ginseng*		*Atp4a*$^{-/-}$ mice	PI3K/AKT/HIF-1α signal pathway	538

B-Asarone	Rhizoma Acori Tatarinowii		MGC803 (IC_{50} = 39.92 μg/mL); SGC7901 (IC_{50} = 84.6 μg/mL); MKN74 (IC_{50} = 96.22 μg/mL)	Reduces the expression of PDK1, PDK4, HIF1α and c-Myc	540
Eleutheroside E	*Acanthopanax senticosus*			Inhibit the Ras-related protein RAP-1A and aerobic glycolysis	543, 544
Chrysin	*Oroxylum indicum* (L.) Vent.		DU145	Promote the degradation of HIF-1α, inhibit the expression of VEGF	545
Wogonin	*Scutellaria baicalensis* Georgi		HCT116 (RF = 2.05)	Inhibit the activation of PI3K/AKT and HIF-1α signal pathway mediated by hypoxia	546
Apigenin	*Apium graveolens* L. Var. Dulce DC.		CD18 (50 μmol/L) S2-013 (50 μmol/L)	Down-regulation of GLUT1 expression depended on the inhibition of HIF-1α	549
Silibinin	*Silybum marianum*		Hepg2 (IC_{50} = 68 μmol/L)	Target GLUT-4 to inhibit glucose uptake	550–552
Xanthohumol	*Humulus lupulus* L.		U87 (IC_{50}~5 μmol/L, 72 h); T98G (IC_{50}~5 μmol/L, 72 h); LN229 (IC_{50}~5 μmol/L, 72 h);	Down-regulating c-Myc and HK2	554
Andrographolide	*Andrographis paniculata* (Burm. F.) Nees		C2C12	Inhibition of NF-κB pathway and glycolytic enzyme HK2	556
Polydatin	*Polygonum cuspidatum* Sieb. Et Zucc.		4T1 (IC_{50} = 66.56 μmol/L); MCF-7 (IC_{50} = 103.1 μmol/L)	Inhibit ROS/PI3K/AKT/HIF-1α/HK2 signal axis	557
Betulinic Acid	*Betula platyphylla* Suk.		MCF-7 (IC_{50} = 19.06 μmol/L); MDA-MB-231 (IC_{50} = 48.55 μmol/L)	Suppresses aerobic glycolysis *via* caveolin-1/NF-kappab/c-Myc pathway	558
Astragaloside IV	*Astragalus membranaceus* (Fisch) Bge. Var. *Mongholicus* (Bge.) *Hsiao*; *Astragalus membranaceus* (Fisch) Bge.		MDA-MB-231/ADR (40 μg/mL); BT-549/ADR (40 μg/mL); MDA-MB-549/ADR (40 μg/mL)	Inhibit hsa_circ_0001982-mir-206/mir-613 axis	560

cancer cells at the gene level, thus inhibiting Warburg effect to limit the proliferation, metastasis and apoptosis of colorectal cancer cells[502]. Interestingly, the new anti-diabetes drug sodium-glucose cotransporter 2 inhibitor canagliflozin has been repurposed for the treatment of liver cancer, which mainly inhibits the uptake of glucose by liver cancer cells in a glucose-dependent manner to inhibit angiogenesis in the tumor, impede the aerobic glycolysis process of liver cancer, and ultimately suppress the growth of cancer cells[503]. The HDAC inhibitor romidepsin can reduce ATP production in a c-Myc dependent manner, while the FAO inhibitors panobinostat or vorinostat can also hinder the occurrence of OXPHOS. The combination of HDAC inhibitors and FAO inhibitors can exert a stronger synergistic effect in GBM compared to single therapy[504]. The structural homolog of tumor suppressor factor p53, TAP73, is overexpressed in human gastric adenocarcinoma cell line AGS-1[130]. Casein kinase 2 (CK2) inhibitor CX-4945 inhibits AGS-1 cell uptake of glucose and release of lactate by inhibiting TAP73 function, inhibits aerobic glycolysis, and ultimately inhibits gastric cancer growth[505,506]. Recently, researchers have discovered a novel potential LDHA inhibitor, 1,3-benzodioxane derivative, which has good anti-proliferative activity against various types of tumor cell lines *in vitro* and may become a potential candidate drug for LDHA inhibitors[507].

5.1.2. *Traditional Chinese medicine (TCM)*

Traditional Chinese medicine plays an irreplaceable role in the comprehensive treatment of tumors, but its efficacy mechanism still needs to be further clarified. The regulation of traditional Chinese medicine on tumor glucose metabolism is a feasible new direction. The diversified components of traditional Chinese medicine make it have the characteristics of multiple pathways and multiple effects. It has unique advantages in the treatment of complex and multifactorial tumor syndrome.

5.1.2.1. Compound recipe and simple recipe. Compound recipe is a classic way of clinical application of traditional Chinese medicine. A few studies have reported the effect of compound recipe on tumor glucose metabolism, which deserves more active and in-depth research. Shenmai liquid was used to treat S180 tumor-bearing mice with spleen deficiency. Shenmai liquid could significantly inhibit tumor growth and reduce the total LDH activity of tumor tissue; Shenmai liquid did not affect the activity of LDH1, but decreased the activity of LDH5, suggesting that the reduction of pyruvate to lactic acid was inhibited[508]. The serum containing Xiaochaihu decoction can promote the differentiation of human hepatoma cell line SMMC-7721 and block the cell in G0/G1 phase. The mechanism is related to the reduction of LDH activity in cells and the up-regulation of SDH activity[509]. Pharmacological studies of single drugs are simpler compared to compound drugs and can consider the characteristics of multiple components and multiple effects of traditional Chinese medicine more comprehensively than single drugs. Therefore, the study of single drug in tumor metabolism is slightly more than that of complex drug. Ginseng oil can reduce the SDH content of SGC-823 gastric cancer cells, suggesting that the tricarboxylic acid cycle may be damaged[510]. Danshen combined with 5-fluorouracil can reduce the microvessel density of Lewis lung cancer tissue in mice. Its mechanism is related to the reduction of HIF-1α mRNA expression in tumor tissue and the down-regulation of VEGF content in serum[511] (Fig. 5B).

5.1.2.2. Monomer of traditional Chinese medicine. Monomer is the most basic component of a single drug. The study of effective monomers of traditional Chinese medicine helps to understand the material basis and mechanism of action of traditional Chinese medicine. Because of its clear structure and ease to accurately quantify, the research on the role and mechanism of monomer in tumor metabolism is more in-depth than that of compound and single drugs (Table 7) (Fig. 5B). The water extract BZL101 of *Scutellaria barbata* D. Don has selective cytotoxicity to breast cancer cells, which is mainly due to inducing breast cancer cells to produce a large number of ROS, which then leads to DNA damage. The excessive activation of poly (ADP ribose) polymerase (PARP) caused by DNA damage further inhibits cell aerobic glycolysis, which shows that LDH activity and lactic acid production are reduced, which ultimately leads to ATP reduction and necrosis[512–514]. Arctigenin selectively induced the necrosis of human non-small cell lung cancer A549 cells which were deprived of glucose. The mechanism was that the inhibition of mitochondrial respiration reduced the cellular ATP content, resulting in the increase of ROS. Glucose deprivation was simulated with aerobic glycolysis inhibitor 2-DG, which had synergistic effect with arctigenin, and had selectivity to tumor cells, but low toxicity to normal cells[515].

Previous studies have shown that PKM2 can play a role as a transcriptional coactivator. Once PKM2 enters the nucleus, it can promote the transcription of target genes, thus promoting the growth of cancer cells and positive feedback regulated aerobic glycolysis[516]. Epoxycaryophyllene is a natural compound widely distributed in plants. It can transform PKM2 into PKM1 by inhibiting aerobic glycolysis, thus exerting its unique anti-cancer effect[517]. At present, clinical research on the treatment of colorectal cancer with epoxycaryophyllene is being carried out. With the in-depth study of the mechanism of Warburg effect of this drug, it may become a new choice for the treatment of colorectal cancer. Inhibition of aerobic glycolysis is one of the anti-tumor mechanisms of oleanolic acid. Oleanolic acid regulates c-Myc-mediated PKM selective splicing by inhibiting the mTOR pathway, resulting in a decrease in PKM2 and an increase in PKM1, and promoting metabolism from aerobic glycolysis to aerobic respiration[518]. Shikonin and its enantiomer alkannin can selectively inhibit the activity of PKM2, and their inhibition of aerobic glycolysis is not affected by the drug sensitivity of tumor, suggesting that they have certain application potential in the treatment of drug-resistant tumors[30]. Cannabinoids play an anti-tumor role by inhibiting the Akt/c-myc pathway to reduce the expression and activity of PKM2, thereby inhibiting aerobic glycolysis and glutamine absorption[519].

HK2 is highly expressed in most cancer tissues, and studying its mechanism in the glycolytic pathway will be a focus of tumor treatment. Arsenic trioxide (ATO) has anti-tumor effect, and inhibiting its activity by binding with HK2 is the mechanism of its inducing apoptosis. Overexpression of HK2 can resist the apoptosis of human gastric cancer SGC7901 cells induced by arsenic. The metabonomic analysis showed that ATO could play a role in promoting apoptosis by inhibiting the activity of HK2 and inhibiting the aerobic glycolysis of tumor[520]. Resveratrol inhibits aerobic glycolysis, ultimately promotes mitochondrial apoptosis,

inhibits cell proliferation, and reduces the resistance of hepatocellular carcinoma to sorafenib, which has a certain synergistic effect[521,522]. It is worth noting that the mechanism of oroxylin A inhibiting tumor aerobic glycolysis is related to cell type and oxygen environment[523,524]. Similarly, the anti-tumor activity of methyl jasmonate is also related to the promotion of HK2 dissociation from mitochondrial VDAC and the reduction of intracellular ATP level[525,526]. Epigallocatechin gallate can inhibit the anchored independent growth of human tongue squamous cell carcinoma in a dose-dependent manner, reduce the expression of HK2 protein by inhibiting AKT pathway to weaken aerobic glycolysis, and inhibit the binding of HK2 with mitochondria to promote apoptosis[527−529]. Curcumin has the effects of growth inhibition and apoptosis induction on human colorectal cancer cells, and HK2 is its important target: by down-regulating the expression and activity of HK2 protein, curcumin down-regulates the aerobic glycolysis of tumor cells, thus inhibiting the production of ATP[530]. It also provides a new perspective for the application of anti-inflammatory Chinese medicine in tumor prevention and treatment.

At present, many traditional Chinese medicine compounds have been found to have regulatory effects on mTOR. Quercetin and ginsenoside Rh4 reduce the expression of aerobic glycolysis-related proteins and inhibit aerobic glycolysis through AKT−mTOR pathway[531,532]. Inhibition of aerobic glycolysis by mTOR is a key step in cardamonin -induced autophagy[533]. Halofuginone is a derivative of halofuginone alkaloid extracted from the Chinese herbal medicine *Dichroa febrifuga* Lour., it exerts its potential anticancer effect by inhibiting Akt/mTORC1 signal transduction and inhibiting aerobic glycolysis pathway. In the tumor cells of colorectal cancer patients treated with halofuginone, mTORC1 and phosphorylated Akt are significantly inhibited, further leading to rapid reduction of hexokinase 2 and glucose transporter 1, thus achieving the effect of inhibiting tumor cell growth[534]. In general, halofuginone inhibits glucose uptake and aerobic glycolysis in colorectal cancer cells by regulating Akt/mTORC1 signal pathway, thus inhibiting the growth of cancer cells *in vitro* and *in vivo*[534].

HIF is an important node of cancer metabolism, and also a research hotspot of cancer metabolism targeted by traditional Chinese medicine. The regulation of Warburg effect by HIF is closely related to PI3K/AKT pathway. Studies have shown that salvianolic acid B, dihydroartemisinin, tanshinone IIA and ginsenoside Rg3 exert antitumor activity by regulating abnormal glucose metabolism through PI3K/AKT/HIF-1α signal pathway[535−538]. Some traditional Chinese medicine compounds have been proved to have multiple targets and pathways in regulating cancer metabolism. For example, cardamonin can not only down-regulate HIF-1α-mediated cell metabolism, but also have a significant impact on glucose uptake and lactic acid production and efflux[539]. β-Asarone reduces the expression of several key genes (PDK1, PDK4, HIF1α, c-Myc, etc.) in aerobic glycolysis, achieving chemosensitivity and inhibition of tumor aerobic glycolysis[540]. It shows that the metabolism of cachexia cannot be separated from the original energy metabolism pathway of cells, and the advantages of multi-molecular target of traditional Chinese medicine may play an advantage in cancer metabolism. ROS is not only a potential mutagen of cancer, but also a factor that stimulates aerobic glycolysis[541]. Carcinogenic K-Ras inhibits mitochondrial respiration by down-regulating mitochondrial respiratory chain complex I, and up-regulates NOX1 production to promote ROS production and HIF accumulation[542]. The effective components eleutheroside E of *Acanthopanax senticosus* can inhibit the Ras-related protein RAP-1A, aerobic glycolysis, and maintain the normal nerve activity of mice with ischemia and hypoxia, but whether it can play a role in tumor cells remains to be further studied[543,544]. Chrysin can promote the degradation of HIF-1α, inhibit the expression of VEGF, and inhibit the angiogenesis of human prostate cancer DU145 transplanted tumor[545]. *In vitro* and *in vivo* experiments showed that wogonin could inhibit the activation of PI3K/AKT and HIF-1α signal pathway mediated by hypoxia, reduce cell glucose uptake, inhibit the expression of glycolytic enzymes HK2, PDK1 and LDHA, and inhibit tumor aerobic glycolysis, thus reversing the hypoxia-induced cisplatin resistance of human colon cancer cells[546]. The inhibition of apigenin on the proliferation and apoptosis of tumor cells was accompanied by the down-regulation of GLUT1 expression. Further research found that the inhibition of celery on GLUT1 expression could reduce the glucose uptake of tumor cells, which depended on the inhibition of HIF-1α to a certain extent[547−549]. Silibinin can also selectively target GLUT-4 to inhibit glucose uptake and exert anti-angiogenic activity and inhibit the growth of cancer cells in a variety of cancers[550−552]. In tumor cells overexpressed with Myc, there will be simultaneous transcription of Myc and HIFα sensitive genes, which will eventually stimulate the conversion of hypoxic aerobic glycolysis[553]. Xanthohumol leads to aerobic glycolysis inhibition by down-regulating c-Myc and subsequent HK2 inhibition[554]. Tanshinone IIA can also inhibit oral squamous cell carcinoma by reducing AKT/c-Myc signal mediated aerobic glycolysis[555].

NF-κB is not only a cancer-promoting factor, but also plays an important role in inflammation and cancer metabolism. It has always been an important target of anticancer drug research. For further exploration of commonly used anti-inflammatory drugs in clinical practice, it may be possible to find effective compounds targeting NF-κB or other inflammatory targets. Inflammation can cause the activation of IKK kinase family, release the transcription factor NF-κB, and ultimately induce the expression of various target genes including HIF1α[556]. *Andrographis paniculata* and *Reynoutria japonica* houtt are commonly used in clinical anti-inflammatory treatment. Andrographolide can significantly reduce the levels of IL-1β and IL-6, and down-regulate the expression of iNOS and COX-2. Its anti-inflammatory effect is related to the inhibition of NF-κB pathway and glycolytic enzyme HK2, but whether it can affect tumor cells requires further investigation[556]. Polydatin inhibits glycolytic phenotype by inhibiting ROS/PI3K/AKT/HIF-1α/HK2 signal axis and enhances its anti-cancer effect[557]. Betulinic acid inhibits aerobic glycolysis of breast cancer cells by regulating Cav-1/NF-κB/c-Myc pathway[558]. In addition, in the study of the reversal mechanism of astragaloside IV on precancerous lesions of gastric cancer, it was found that astragaloside IV can reduce abnormal aerobic glycolysis by regulating the expression of p53, TIGAR and other related glycolytic proteins[559]. It could also reverse the drug resistance of TNBC by blocking the hsa_circ_0001982-miR-206/miR-613 axis and inhibiting aerobic glycolysis[560].

5.2. *Combination strategies*

Tumor metabolism involves multiple genes and pathways with complex regulation. Inhibition of a single signal pathway or a single target may not be sufficient to treat tumor, and may even

lead to drug resistance. Activation of bypass pathway is one of the important reasons. To overcome the drug resistance caused by the activation of the bypass, at present, the way of combining multiple signal pathway inhibitors horizontally is mostly adopted. In addition, because each signal pathway will ultimately affect the cell behavior by regulating the downstream metabolism, the longitudinal combination of signal pathway and metabolic pathway inhibitors may also produce enhanced anti-tumor effect. Therefore, exploring the complementary metabolic pathway targeted by combination therapy may enhance or synergistically inhibit the survival of tumor cells. With the introduction of the hybrid OXPHOS/glycolytic metabolism model, a new idea for the comprehensive treatment of tumor metabolism has been proposed. *In vitro* experiments confirmed that metformin combined with aerobic glycolysis inhibitor 2-DG can activate AMPK and reduce the phosphorylation of mTORC1-regulated protein A, and induce cancer cell death at both cellular and animal levels, providing a preliminary basis for comprehensive targeted inhibition[500]. It is suggested that combined inhibition of aerobic glycolysis and OXPHOS activity in tumor cells, along with precise blocking of their metabolic pathways, may eliminate the metabolic plasticity of tumor cells and enhance the efficacy of tumor metabolic regulation therapy. Metformin and fasting therapy can cooperate to inhibit tumor growth through PP2A−GSK3β−MCL-1 pathway, but their safety requires further experimental confirmation[562]. In addition, the combination of chemotherapy drugs and metabolic-targeted therapeutic drugs can reduce the dose of chemotherapy drugs and the adverse reactions of chemotherapy. On the other hand, it can regulate the metabolic mode of tumor cells, overcome the chemotherapy resistance of tumor cells, and improve the treatment efficacy of tumor patients. This will be a promising treatment strategy[563]. For example, shikone, a small molecule active substance, can prevent tissue plasminogen activator (TPA) mediated skin cells from transforming into cancer at an early stage by inhibiting PKM2. It can repair the damage of mitochondrial function caused by TPA, reduce the production of lactic acid, an aerobic glycolysis marker, and also overcome the resistance of bladder cancer to cisplatin through mediating necrosis[463,564]. The AMPK inducer AICAR and methotrexate (MTX) often produce drug resistance when used alone in breast cancer. One study found that the combination of the two can block the aerobic glycolysis process by promoting mitochondrial oxidation, inhibit the occurrence of warburg effect, and finally reverse the phenomenon of slow proliferation of breast cancer cells[565] (Fig. 5C).

5.3. New strategies

With the development of modern molecular biology technology and the development of targeted gene research, the importance of aerobic glycolysis pathway in tumor cell growth, invasion and other processes has been ignored for a long time. In recent years, fluorodeoxyglucose positron emission tomography (FDG-PET) technology based on the "Warburg effect" has made the research on tumor energy metabolism rise again. Using this PET imaging technology to detect patients, we can judge the location of the primary tumor and metastatic tumor in the body by where the glucose uptake in the body is significantly enhanced, providing a means for efficient and specific diagnosis and efficacy monitoring of tumors[566]. As a highly metastatic and fatal subtype of breast cancer, triple-negative breast cancer (TNBC) remains an unresolved challenge in clinical identification and diagnostic imaging[401,567,568]. GLUT1 inhibitor probe provides a potential use for aerobic glycolysis diagnostic imaging of TNBC[569]. However, due to the low contrast of imaging due to impaired physiological aerobic glycolysis, FDG/PET diagnostic results are not ideal, and more sensitive and accurate identification is still required[570]. GLUT1 and GLUT3 transport glucose analogues FDG into tumor cells[571], while the decreased sensitivity of FDG-PET detection in the diagnosis of liver cancer leads to abnormal expression of GLUT2 in liver cancer tissue[572]. Unfortunately, the role and mechanism of GLUT2 in the development of liver cancer are still unclear. PET/CT integrates FDG-PET images with CT images to make tumor localization more accurate. Due to differences in GLUT-1 expression on various types of cancer cell membranes, its applicability is limited. Mucous adenocarcinoma, signet ring cell carcinoma and poorly differentiated cancer tissue have low expression of GLUT-1, and the uptake of glucose is less than that of intestinal cancer[559]. In addition, the tumor size, stage and the degree of gastric expansion will affect the FDG uptake. Compared with gastroscopy and enhanced CT, its sensitivity and specificity are poor. Although PET/CT has poor sensitivity in detecting primary lesions, it is of great significance in evaluating microsatellite instability of cancer, asymptomatic progressive cancer and neoadjuvant treatment of cancer, especially neoadjuvant treatment[573]. In order to improve the sensitivity and specificity of PET/CT, there are currently new tracers such as ^{18}F-FLT targeting proliferation, ^{18}F-FMISO targeting tumor hypoxia, and radiolabeled choline derivatives targeting phosphate metabolism[574]. magnetic resonance imaging (MRI) with new sequence has outstanding performance in primary tumor and lymph node staging, and PET/MRI has more advantages in detecting tumor, lymph node and distant metastasis[575].

Warburg effect has been confirmed in different types of tumors, and FDG-PET has been used to detect cancer cells and applied to clinical practice. However, there are potential limitations when FDG-PET is used to detect certain types of cancer, such as colorectal cancer, that is, there are some false positives, which may lead to some colorectal cancer patients being wrongly judged by FDG-PET when detecting disease recurrence. Nevertheless, with the advent of "one-stop shop" imaging and contrast enhanced FDGPET, the integration of new PET trackers and PET magnetic resonance imaging (MRI), it may play an increasing role in the evaluation and management of cancer patients. The metabolic reprogramming property of tumor cells can enhance the aerobic glycolysis process, which is mainly manifested in the tumor microenvironment and is closely related to the down-regulation of mitochondrial H^+-ATPase catalytic subunit. It can be used as a pre-indicator of patients by detecting the glucose metabolism in tumor cells. The further study on the relationship between FDG-PET, PET-MRI and cancer cell metabolic reprogramming characteristics and Warburg effect will provide a new direction and idea for clinical detection of cancer (Fig. 6A).

5.4. Potential strategies

Nowadays, cancer targeted therapy has become an inevitable trend of precision medicine. However, the target of targeted therapy mainly focuses on cancer mutation genes and pathways, which severely limits the types of drug targets. Mutations that lead to the development of cancer will also bring about weaknesses that can be used for treatment. Drug treatment of cancer also depends on such a concept. Large-scale cancer genome sequencing has classified mutations of various cancer types, which can be used to explore the vulnerability of cancer. These gene changes include

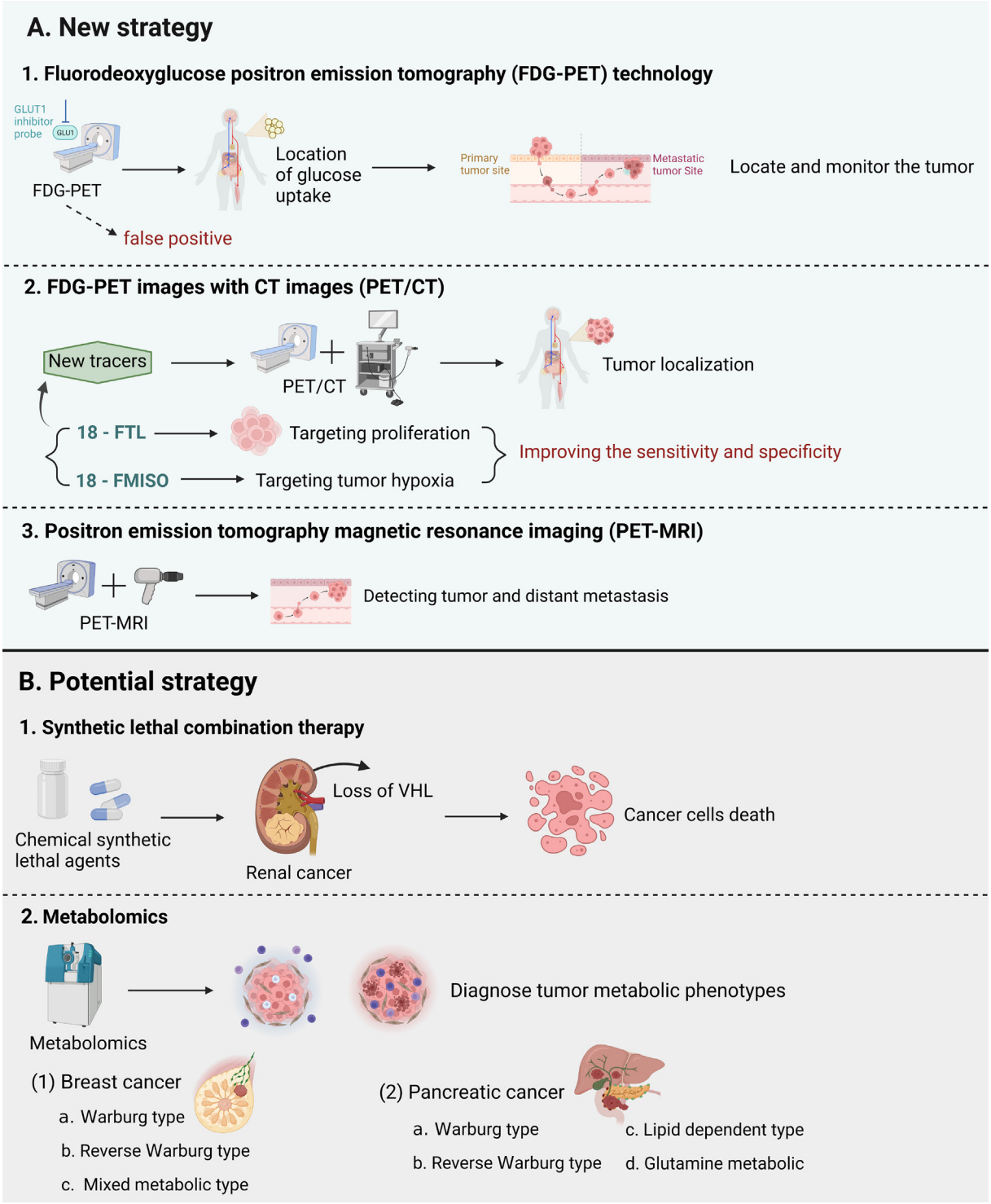


Figure 6 New and potential strategies for cancer treatment targeting the Warburg effect. (A) New strategies include fluorodeoxyglucose positron emission tomography (FDG-PET) technology, FDG-PET images with CT images (PET/CT) technology, and positron emission tomography magnetic resonance imaging (PET-MRI) technology. (B) Potential strategies involve synthetic lethal combination therapy and metabolomics which is used for tumor typing.

functional acquisition mutations (gene amplification, translocation or mutation) and functional loss mutations (gene function is impaired due to missense mutations or deletions). The concept of synthetic lethality, that is, the presence of cancer gene mutations is usually associated with a new vulnerability that can be targeted for treatment, can help us greatly expand the arsenal of potential cancer drug targets. Cancer cells usually maintain metabolic activity and resist anti-glycolytic therapy through metabolic reprogramming. Therefore, synthetic lethal combination therapy is crucial to reduce the therapeutic effect of Warburg metabolism. A

study found that chemical synthetic lethal agents for the loss of VHL in renal cancer are usually lethal to cancer cells with high GLUT1 levels and need aerobic glycolysis[82], suggesting that the method of screening compounds with lethal synthesis may also be applicable to other tumor types with loss of tumor suppressor gene function or functional gain of oncogene.

Additionally, individualized precise treatment can be tailored based on the different molecular typing and metabolic characteristics of tumor cells. As a new technology, metabonomics aims to study the abnormal metabolic patterns of tumors, and has shown great potential in the diagnosis of metabolic typing and individualized treatment of tumors. According to the metabolic differences between breast cancer tumor cells and stromal cells, researchers divided them into four metabolic phenotypes: Warburg type (tumor cells show aerobic glycolysis characteristics, while stromal cells do not); reverse Warburg type (stromal cells have glycolytic characteristics, but tumor cells do not); mixed metabolic type (both tumor cells and stromal cells have glycolytic characteristics); no marker type (tumor cells and stromal cells have no aerobic glycolysis characteristics[500]. According to the different metabolic phenotypes of tumor cells, pancreatic cancer can be divided into Warburg type, reverse Warburg type, lipid-dependent type and glutamine metabolic type[576]. The research and application of metabolic typing provide a metabolic basis for more effective tumor metabolic intervention. Currently, research on metabolism primarily focuses on *in vitro* cultured cells and tissues. The culture environment of *in vitro* cultured cells cannot accurately reflect the true situation of the *in vivo* environment. During the processing of *in vitro* tissues, rapid changes such as ischemia and hypoxia can lead to drastic changes in cell metabolism, and it is difficult to reflect the in situ metabolic changes of living tissue cells in animals. Therefore, it is urgent to develop new metabolite labeling techniques, in situ non-destructive testing of proteins and metabolites, and micro detection techniques. Glucose metabolism markers can also be applied to targeted tumor therapy by modifying tumor cells and immune cells[577–580]. Among them, based on the self-modification of tumor cells, specific antigens can be artificially added to the surface of tumor cells to increase their targeting. For example, known haptens can be added to the surface of tumor cells, which can activate anti-tumor immunity through hapten carriers[577]. Additionally, it can link antigen target molecules of marketed tumor-specific antibody drugs, potentially addressing the dilemma of TNBC and other tumor types without drugs available[579]; Alternatively, by modifying specific antigens and using their paired antibodies to develop CAR-T cells, personalized tumor immunotherapy can be achieved[580]. As T cell and NK cell immunotherapy advances, modifications based on glucose metabolism markers can enhance target selectivity for CAR-T, TCR-T, and CAR NK cell therapies. However, due to the complexity of metabolic markers and the lack of cross-validation, a long road remains toward achieving fully standardized treatment.

Cancer cells meet their energy and biosynthesis needs by altering their own metabolic characteristics and enhancing aerobic glycolysis, which can promote cancer cell proliferation, reduce drug-induced cell apoptosis, and thus develop cancer resistance. A large amount of evidence suggests that metabolic disorders in cancer cells are closely related to cancer resistance during cancer treatment. For example, LDHA is associated with paclitaxel/trastuzumab resistance in the treatment of breast cancer[581]. PDK3 is associated with hypoxia-induced drug resistance in the treatment of cervical and colon cancer[582]. Fatty acid synthase (FAS) is associated with docetaxel/trastuzumab/doxorubicin resistance in the treatment of breast cancer, and gemcitabine and radiotherapy resistance in the treatment of pancreatic cancer[80]. GLS is associated with cisplatin resistance in the treatment of gastric cancer[77]. The molecular mechanisms underlying cancer drug resistance caused by metabolic disorders in cancer cells are extremely complex. The combination of GLUT1 inhibitor WZB117 and cisplatin or paclitaxel can also demonstrate synergistic anticancer effects[583]. Ritonavir can also inhibit the proliferation of primary myeloma cells and increase the sensitivity of cancer cells to doxorubicin[584]. The combination of HK2 inhibitor 2-DG and ABT-737 can improve ABT-737 resistance[585]. In clinical trials, the combination of PDK inhibitor dichloroacetate (DCA) and omeprazole has shown synergistic anticancer efficacy[586]. GLS1 inhibitor dimethyl-2[-5-phenylacetyl-1,2,4-thiadiazo-2-yl] ethyl sulfide (BPTES) can improve the therapeutic efficacy of mutant IDH1 patients[587]. The combination of FAS inhibitor G28UCMM, trastuzumab and lapatinib showed a good synergistic effect[588]. The aerobic glycolysis of malignant tumor cells is also closely related to tumor radiation resistance[589,590]. A study has confirmed that in hypoxic malignant tumors, reducing lactate content and increasing oxygen consumption based on the Warburg effect can increase their sensitivity to fractionated radiotherapy and improve patient prognosis[591]. These research results indicate a close relationship between metabolic disorders in cancer cells and resistance to cancer. Targeting key enzymes in the metabolic process of cancer cells can be used to improve cancer resistance and enhance the efficacy of chemotherapy drugs in cancer patients. However, the molecular mechanism underlying cancer resistance caused by metabolic disorders is not fully understood and further research is needed. The combination of cancer chemotherapy and anti-metabolic therapy, combined with individualized treatment concepts, will further improve the efficacy of cancer patients (Fig. 6B).

6. Discussions

Activation of oncogenes and the deletion of tumor suppressors promote metabolic reprogramming in cancer, leading to increased nutrient absorption for energy and biosynthetic pathways. Thus, metabolic reprogramming is considered a characteristic of cancer[29]. Cancer cells utilize a higher rate of aerobic glycolysis to ingest glucose for metabolic synthesis, providing an evolutionary advantage and more biosynthetic substances for tumor cell growth and reproduction[353]. This energy metabolism characteristic, known as the Warburg effect, plays a crucial role in maintaining high proliferation rates and increasing anti-apoptotic characteristics in cancer cells[28].

During cancer occurrence and development, the Warburg effect influences the evolution of cancer by affecting the energy metabolism of cancer cells, particularly the aerobic glycolysis pathway, and by participating in the expression of common transcription regulatory factors and proteins such as FOXM1, p53, NF-κB, HIF1α, and c-Myc. Key enzymes involved in the Warburg effect include GLUTs, HKs, PFKs, LDHs, and PKM2, which significantly contribute to cancer occurrence and development. High expression of these key glycolytic enzymes in patients is associated with distant metastasis, deeper tumor invasion, and later clinical stages.

LncRNAs, miRNAs, and circular RNAs play crucial roles in regulating the glucose metabolism of cancer cells by targeting

genes involved in metabolism, thereby promoting cancer cell growth, proliferation and metastasis[232]. Limiting the energy intake of tumor cells as a strategy for cancer treatment and prevention has garnered increasing interest among scientists. This concept has shown remarkable results in animal and human experiments[592,593]. The principle of taking energy metabolism as an anti-tumor strategy mainly depends on the difference of energy production mechanism between normal cells and transformed cells[594]. However, the differences in energy production mechanisms between normal cells and cancer cells must be considered when using energy metabolism as an anti-tumor strategy. Tumor cells are highly vulnerable to limitations in energy supply, making them an attractive target for further research on factors or substances that can influence the Warburg effect and affect the growth, reproduction, and metastasis of cancer cells.

Traditional Chinese medicine offers multiple channels and effects in the comprehensive treatment of tumors due to the cooperation, synergism, and network interactions between its diversified components. However, it also poses challenges in terms of efficacy, pharmacological mechanism, and drug interactions. Tumor cells exhibit metabolic heterogeneity due to differences in genotypes, types, degrees of differentiation, stages, and microenvironments. The metabolic coupling between tumor cells and the tumor microenvironment can induce changes in tumor cell metabolism, enabling effective adaptation to external stress and facilitating malignant progression. Therefore, targeted tumor metabolic therapy requires accurate diagnosis and individualized typing detection. Treatment should be selected based on the metabolic dependence and specific metabolic phenotypes of tumor cells, leading to different intervention measures and the transformation of metabolic phenotypes to achieve the best therapeutic effect.

Metabolic reprogramming is also an important feature of tumor drug resistance. Understanding the metabolic process underlying drug resistance in tumor cells can shed light on the molecular mechanisms involved. Uncontrolled metabolic processes have been found to overcome drug resistance in tumor cells, and inhibitors targeting metabolic enzymes have shown significant effects in reversing tumor drug resistance, with some entering phase I clinical trials. Discovering molecular markers related to drug resistance can accurately predict drug resistance, metastasis, and prognosis in tumors. Metabonomics has enabled more efficient and systematic studies on the reprogramming of metabolic networks in drug-resistant tumor cells.

The Warburg effect, originally used to describe increased lactic acid production in cancer, has enduring research significance and has been found to play important roles in regulating various life activities, including immunity, angiogenesis, pluripotency, reproduction, pathogen infection, macrophage polarization, and T cell activation[595−598]. Exploring the multi-target comprehensive treatment potential of the Warburg effect is worth further investigation[599,600]. By reducing the activity of enzymes related to aerobic glycolysis or controlling energy supply through dietary means, tumor cells can be exposed to a prolonged energy-deficient microenvironment. Understanding aerobic glycolysis has confirmed the potential for targeted therapy of metabolic changes in tumor cells, and recent studies have identified numerous potential pathways and targets for cancer treatment. Each tumor type has its own unique metabolic pathway, with most tumors exhibiting characteristics of the Warburg effect. While research on targeted therapy has focused mainly on key enzymes and rate-limiting enzymes in aerobic glycolysis and glutamine metabolism, limited research has been conducted on key enzymes in the TCA cycle. It is believed that more potential therapeutic targets will be discovered in the future. Challenges in targeted tumor metabolism include the non-specific tropism of metabolic inhibitors and their potential inhibition of immune cells, making combination therapy with metabolic inhibitors more effective in clinical practice.

Overall, cancer cells exhibit accelerated growth, proliferation, and metastasis pathways through the involvement of oncogenes, key enzymes, metabolic pathways, and other metabolic mechanisms. The mechanism of cancer occurrence and development, particularly its relationship with the Warburg effect, remains unclear and requires further exploration. In-depth studies on the relationship between the Warburg effect and cancer can provide new directions and approaches for the early diagnosis and treatment of cancer patients.

Acknowledgments

This work was supported in part by National Natural Science Foundation of China (Grant No. 82172649, 82003580, and 82173666), and Shenzhen science and technology research and development funds (Grant No. JCYJ20210324094612035, China).

Author contributions

Bo Liu, Dahong Yao and Jin Zhang conceived the project and supervised the project. Jin Zhang provided the new idea. Minru Liao drafted the tables and manuscript. Lifeng Wu draw the figures. Jin Zhang and Zhiwen Wang proofread the structure and figures. Bo Liu and Chaodan Luo polished the manuscript. All the authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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