Advances of HIF-1α/glycolysis axis in non-small cell lung cancer (Review)

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Abstract. It is now widely accepted that there is a specific metabolic pattern in tumor cells termed the Warburg effect, which causes tumor cells to tend to use glycolysis for energy. Hypoxia-inducible factor (HIF) 1α is involved in these metabolic patterns as a key molecule promoting glycolysis. In addition, there is now increasing evidence that targeting this metabolic pattern of the tumor to cut off the energy source of the tumor tissue is an effective therapeutic modality. However, different molecules are involved in the regulation of the HIF-1α/glycolysis axis in different tumor tissues. This review focused on non-small cell lung cancer (NSCLC) to elucidate the currently known signaling pathways centered on the HIF-1α/glycolysis axis and to identify the key molecules that can serve as therapeutic targets. It also summarized the effective methods of treatment of NSCLC by inhibition of HIF-1α/glycolysis that have emerged in recent years.

Contents

1. Introduction
2. Regulation of HIF-1α expression in NSCLC
3. Regulatory mechanism of HIF-1α/glycolysis axis in NSCLC
4. Progress in targeting the HIF-1α/glycolysis axis for NSCLC treatment
5. Conclusions

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Introduction

Lung cancer is considered being one of the most threatening malignant tumors in the health and life of individuals, with the highest fatality rate in the world (1). It can be histologically divided into two categories: Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), of which NSCLC accounts for ~85% (2). NSCLC is characterized by lack of symptoms when tumors are small in the early stages, so most patients have locally advanced or metastatic lesions at diagnosis (3). Therefore, it is of great importance to understand the mechanism of NSCLC development to guide the development and use of lung cancer-targeted drugs, including the combination of clinical drugs.

In the past decade, scholars have generally recognized the importance of tumor-specific metabolic patterns in the pathogenesis of tumors. Among them, the Warburg effect indicates that tumor cells tend to obtain energy through aerobic glycolysis along with lactate production, even in the presence of oxygen (4). In addition, hypoxia is an important feature of solid tumors and induces cells to undergo glycolysis to produce energy (5). Therefore, efficient glycolysis is the main function of tumor cells. The occurrence of this phenomenon depends on the regulation of intracellular oncogene and tumor suppressor gene signaling pathways on cellular metabolic pathways. The central regulator in the above regulatory process is the hypoxia-inducible factor (HIF) (6).

HIF is a type of transcription factor that is rapidly produced and accumulated in the cell environment under hypoxic conditions. It was initially discovered that it can significantly increase the transcription of erythropoietin by interacting with its enhancer (7). HIF is a heterodimer consisting of one α-subunit and one β-subunit. It is currently known that there are three types of both a-subunit and β-subunit which are HIF-1α, HIF-2α, HIF-3α, HIF-1β, HIF-2β and HIF-3β (8). Among them, HIF-1α is the most oxygen-sensitive active subunit, which is the main part of HIF-1 to fulfill its function, and it is the earliest discovered and the more thoroughly studied subunit at present (9). Under physiological conditions when oxygen supply is sufficient, HIF-1α is easily degraded by the proteasome through the complex formed by oxygen-dependent hydroxylation and E3 ubiquitin ligase, so its half-life is only 5-10 min (10). As a result, signaling pathways

downstream of HIF are not activated and transcription of the more than 40 genes it regulates, including erythropoietin, glucose transporter proteins, glycolytic enzymes, vascular endothelial growth factor and other genes and protein products that increase oxygen delivery or promote hypoxic metabolism, is at a low level (11).

Generally, regulation of HIF-1α expression is complex and can be categorized into oxygen-dependent and oxygen-independent components. The oxygen-independent mechanisms include the transcription regulation of HIF-1α expression through the action of transcription factors such as nuclear factor-κB (NF-κB), specificity protein 1 (SP1) and signal transducer and activator of transcription 3 (STAT3) (12). The actions of these transcription factors are in turn regulated by reactive oxygen species (ROS), cytokines and/or lipopolysaccharide (LPS)-dependent signaling-activated protein kinase C (PKC), NF-κB kinase inhibitor (IKK), and/or phosphatidylinositol 3-kinase (PI3K) pathways (13). HIF-1α protein translation can be regulated by microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and/or angiotensin II-mediated signaling involving PI3K. The oxygen-dependent mechanism affecting the half-life of HIF protein in the normal state is mainly due to the von Hippel-Lindau protein (pVHL) degradation pathway. In this degradation pathway, pVHL catalyzes the ubiquitination of the hydroxylated HIF-1α (14). While hydroxylation of the HIF-1α is catalyzed by two currently known enzymes, prolyl hydroxylase domain-containing proteins (PHDs) and asparagine hydroxylase factor inhibiting HIF (FIH) (15,16), their activity is reduced by a decrease in oxygen tension and thus the stability of the HIF-1α is affected by oxygen tension.

From the clinical data, HIF-1α is highly expressed in NSCLC and is strongly associated with poor clinical prognosis (17-19). Therefore, studying the role of HIF-1α in NSCLC is of great significance for NSCLC treatment. The current review focused on HIF-1α mediated glycolysis in NSCLC, described the intracellular regulatory mechanisms and summarized how they affect the development and treatment of tumors.

2. Regulation of HIF-1α expression in NSCLC

A number of clinical investigations have shown that the positive rate of HIF-1α expression in NSCLC is significantly higher (up to 15-20 times) than that in normal tissues (20-22). This phenomenon is closely related to the molecular signaling and cells in the tumor microenvironment described in the following sections.

Molecular signaling regulating HIF-1α level. Several molecules that are differentially expressed in NSCLC compared with normal cells can alter the HIF-1α expression in NSCLC by affecting the transcription, translation or protein degradation of HIF-1α (Fig. 1). In the HIF-1α protein degradation signaling pathway, it has been found that in primary NSCLC, the content of intracellular HIF-1α and the expression of its downstream genes are positively correlated with the expression of PHD protein family (23). Aldolase A is also highly expressed in NSCLC and is positively correlated with the expression of HIF-1α in the nucleus. It can cause HIF-1α accumulation by promoting the release of lactic acid, which causes the decrease in PHD activity (24). ROS can also inhibit PHD to stabilize HIF-1α (25) and the depletion of intracellular succinate dehydrogenase 5 in high glucose environment leads to the accumulation of ROS and the increase of HIF-1α protein level (26) (Fig. 1 left; bottom orange section).

The main factor on the transcriptional regulation of HIF-1α is STAT3 signaling pathway (Fig. 1 left; top green section) in NSCLC. The JAK2/STAT3 pathway is inhibited by miR-337-3p, which is downregulated in NSCLC. At the same time, circular (circ)RNA zinc finger protein 124 is highly expressed and binds with miR-337-3p to further weaken its inhibitory effect on JAK2/STAT3 pathway (27). In addition, Ras-related protein Rab-17 is downregulated in NSCLS, which could reduce the inhibition of STAT3 phosphorylation (28). The non-coding (nc)RNA TSLNC8 is also downregulated, which can inhibit the IL-6/STAT3 signaling pathway. Taken together, all these three signaling pathways can promote the transcription expression of HIF-1α via STAT3 pathway in NSCLC cells (29).

The translational regulation of HIF-1α is promoted by eukaryotic initiation factor 4G1(eIF4G1) and mTOR signaling pathways (Fig. 1 left; middle blue section). Eukaryotic initiation factor complex F4 (eIF4F) includes eIF4G1 and eIF4E. MET significantly increases the phosphorylation level on Ser-1232 of eIF4G1 via MAPK, which leads to the translational expression of HIF-1α (30). Activation of PI3K/AKT/mTOR pathway also promotes HIF-1α translation. Retinoblastoma binding protein 2 (RBP2) is highly expressed in NSCLC and is associated with poor prognosis. By stimulating this pathway, RBP2 can upregulate the expression of HIF-1α to promote the growth of tumor blood vessels (31).

Cells in tumor microenvironment affecting HIF-1α level. Several types of cells in the tumor cell microenvironment are also involved in the regulation of HIF-1α expression inside NSCLC (Fig. 1 right panel). Cancer-associated fibroblasts (CAFs) are important stromal cell components in the solid tumor microenvironment and significantly accelerate the proliferation, invasion and epithelial-mesenchymal transition of NSCLC cells (32). miR-224 is significantly upregulated in both CAFs and CAFs co-cultured NSCLC cells and Sirtuins 3 (SIRT3)/AMPK axis is inhibited by miR-224-targeted SIRT3 untranslated region in NSCLC, thereby activating mTOR and increasing HIF-1α expression. In turn, high levels of HIF-1α can promote the high expression of miR-224, forming a positive feedback loop (33). Mesenchymal stem cells (MSCs)-derived exosomal miR-204 acts on Krüppel-like factor 7 (KLF7) in NSCLC to downregulate the KLF7/AKT/mTOR/HIF-1α axis to play an anticancer role (34). M2 macrophage-derived extracellular vesicles regulate the Hippo/HIF-1 axis to enhance the cell viability and migration ability of NSCLC under hypoxic conditions (35).

3. Regulatory mechanism of HIF-1α/glycolysis axis in NSCLC

As HIF-1α is a transcription factor, its activation can promote the transcription of multiple genes, including energy metabolism, angiogenesis and apoptosis, among which glycolysis-related

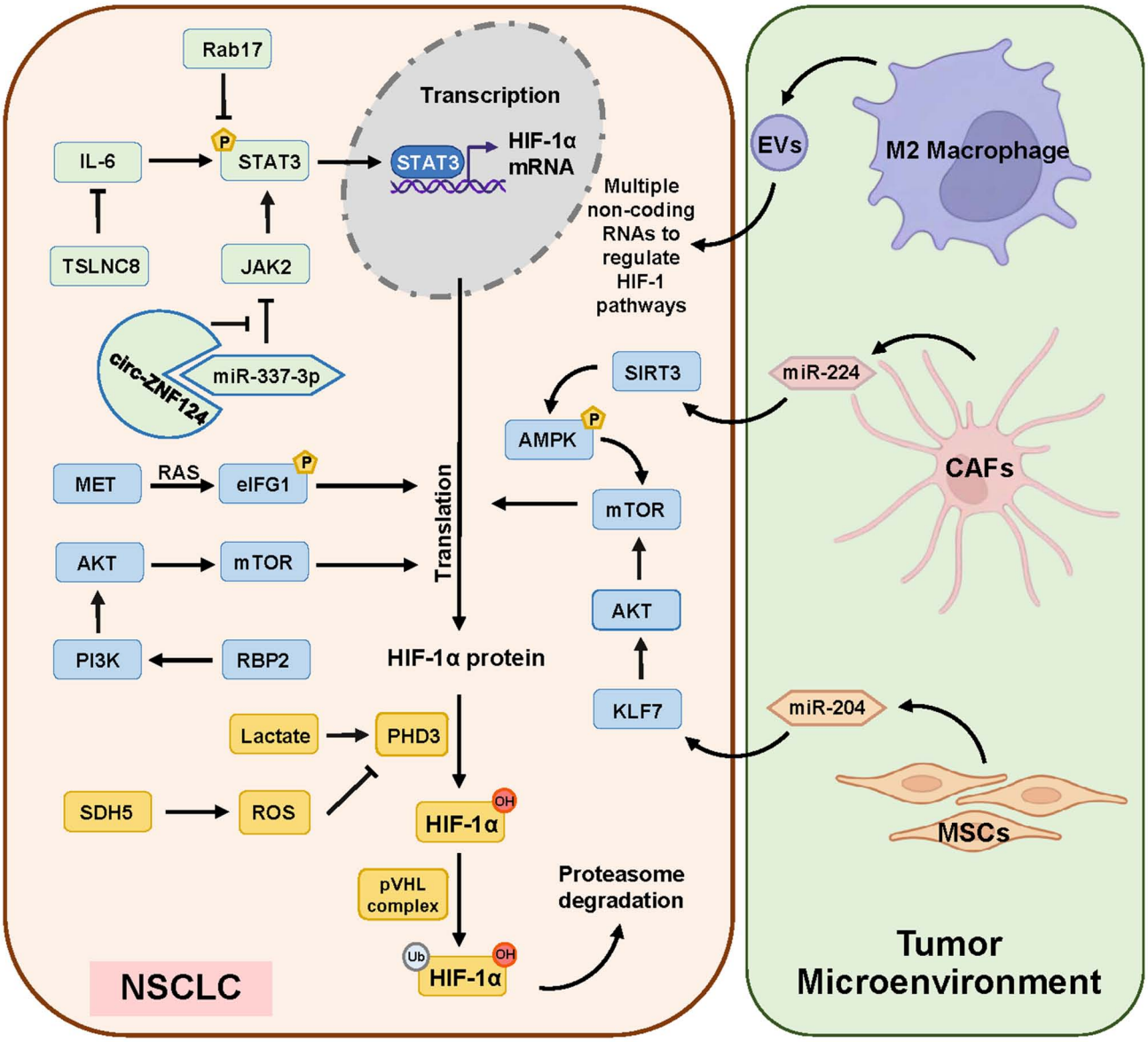

Figure 1. Molecular signaling and cells in tumor microenvironment regulating HIF-1α level in NSCLC. Currently demonstrated data show that STAT3 plays a major role in the transcriptional regulation of the HIF-1α expression (green). The pathways that promote the translation regulation of HIF-1α are mainly the PI3K/AKT and the mTOR pathways (blue). The enzymes PHD3 and pVHL influence the promotion of ubiquitinated degradation of HIF-1α (orange). Several types of cells in the tumor cell microenvironment are also involved in the regulation of HIF-1α expression inside NSCLC (right panel). HIF-1α, hypoxia-inducible factor 1α; NSCLC, non-small cell lung cancer; PHD3, prolyl hydroxylate 3; pVHL, von Hippel-Lindau protein; miR, microRNA; circ, circularRNA; ROS, reactive oxygen species; RBP2, retinoblastoma binding protein 2; SDH5, succinate dehydrogenase 5; KLF7, Krüppel-like factor 7; EVs, extracellular vesicles; CAFs, cancer-associated fibroblasts; MSCs, mesenchymal stem cells.

genes are the most important in NSCLC. The currently known ways in which HIF-1α promotes glycolysis can be simply classified into three aspects: Promoting glucose uptake by cells, inhibiting the tricarboxylic acid (TCA) cycle and regulating the activity of glycolysis-related enzymes. The following are the signaling pathways regulated by HIF-1α found in the field of glycolytic metabolism in recent years.

ncRNAs alterations as initiating factors of HIF-1α/glycolysis axis. ncRNAs play an important regulatory role in HIF-1α-mediated glucose metabolism. Among them, miRNA, circRNA and lncRNA are common molecules involved in the regulation (Fig. 2). miR-182 promotes the mRNA expression of glycolysis-related enzymes alpha-enolase, glucose transporter 1 (GLUT1), hexokinase (HK) 1, HK2, lactate dehydrogenase (LDHA) and pyruvate dehydrogenase kinase-1 (PDK1) by upregulating HIF-1α (36). In addition, miRNA-31-5p overexpressed in NSCLC targets HIF-1α inhibitors to increase the activity of HIF-1α and then increase the expression of GLUT1, GAPDH, and LDHA to promote glycolysis (37). Meanwhile, miRNA-199a is downregulated in NSCLC, which reduces its target inhibitory effect on HIF-1α, causing the increased expression of HIF-1α. This further increases the expression of PDK1 to inhibit the TCA cycle (38).

In addition to the regulatory effect of changes in the expression of miRNAs themselves, some circRNAs can indirectly regulate the HIF-1α/glycolysis axis by

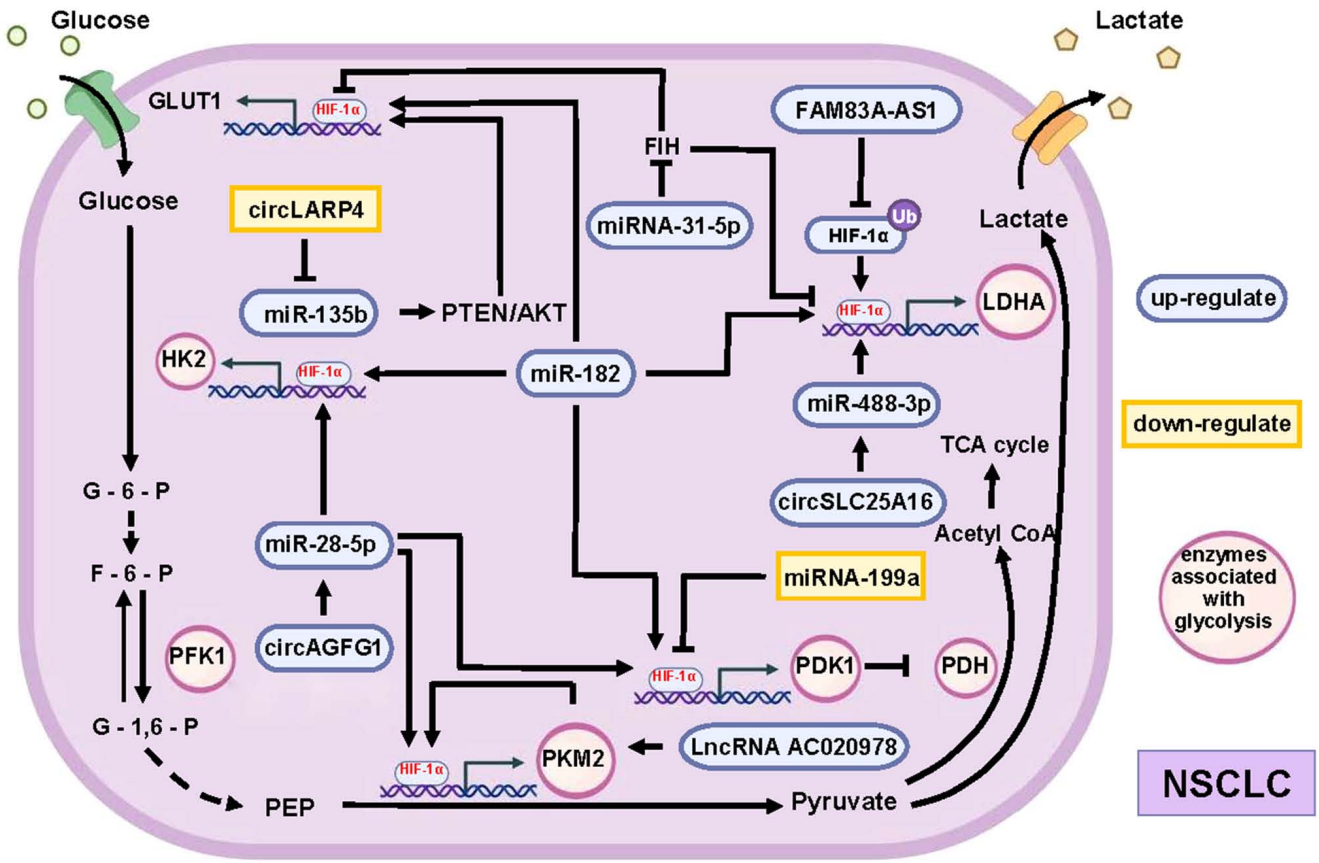

Figure 2. Non-coding RNAs alterations as initiating factors of HIF-1α/glycolysis axis. Various non-coding RNAs can affect the expression of glycolysis-related enzymes by altering the expression of HIF-1α, and these different pathways work together to promote glycolysis in NSCLC. Compared with normal cells, the expression of these non-coding RNAs is altered in NSCLC, with some upregulated (purple) and others downregulated (orange). The roles of different non-coding RNA expression changes in promoting the expression of all key enzymes of HIF-1α-mediated glycolysis are synergistic and complementary. For example, the increase in HK2 expression is facilitated by the increase in miR-182 and miR-28-5p content. At the same time, the increased levels of miR-182 and miR-28-5p also synergizes with the decreased levels of miRNA-199a to promote PDK1 expression. HIF-1α, hypoxia-inducible factor 1α; NSCLC, non-small cell lung cancer; HK, hexokinase; miR, microRNA; PDK1, pyruvate dehydrogenase kinase-1; circ, circularRNA; PFK1, phosphofructokinase; lnc, long non-coding; LDHA, lactate dehydrogenase; PKM2, pyruvate kinase 2; TCA, tricarboxylic acid; acetyl CoA, acetyl coenzyme A; PDH, pyruvate dehydrogenase.

regulating the expression of miRNAs. Among the upregulated circRNAs, circSLC25A16 and circAGFG1 promote glycolysis via miR-488-3p/HIF-1α/LDHA (39) and miR-28-5p/HIF-1α/GLUT1, phosphoglycerate kinase 1 and Pyruvate kinase M2 (PKM2) (40), respectively. Exosomal circSHKBP1 promotes the expression of PKM2 by inhibiting miR-1294 (41). PKM2 can not only accelerate glycolysis as a key enzyme but also promote the expression of HIF-1α-dependent glycolytic enzymes by activating HIF-1α (42). In addition, the expression of circLARP4 reduces the activity of HK2 and reduces the amount of glucose uptake and lactate excretion by cells. Downregulation of circLARP4 affects the miR-135b/PTEN/AKT/HIF-1α axis to promote glycolysis in NSCLC (43).

Furthermore, lncRNA-AC020978 is upregulated during hypoxia, increasing the stability of PKM2 by directly interacting with PKM2 to participate in the regulation of PKM2-enhanced HIF-1α transcription activity (44). lncRNA FAM83A-AS1 promotes glycolysis by inhibiting the ubiquitination of HIF-1α, which accumulates in cells and then promotes the expression of HK2 and LDHA (45).

Protein molecules alterations as initiating factors of HIF-1α/glycolysis axis. Several protein molecules are involved in specific HIF-1α-dependent regulation of glycolysis in NSCLC (Fig. 3). Part of the mechanism is centered on the altered expression of HK2 as the core of regulation. Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) is a fusion protein found in 3-7% of NSCLC. EML4-ALK induces hypoxia-independent but glucose-dependent accumulation of HIF-1α via both transcriptional activation of HIF-1α mRNA and the PI3K-AKT pathway to enhance HIF-1α synthesis. In addition, the high expression of EML4-ALK promotes the binding of HIF-1α to HK2 promoter, which increases the expression of HK2 to promote glycolysis (46). Tumor necrosis factor receptor-associated factor 6 (TRAF6) is achieved by direct activation of AKT, which also causes the upregulation of HIF-1α/HK2 and promotes glycolysis (47).

Another key enzyme is PKM2. ERK in the MAPK signaling pathway promotes the endonuclear translocation of low-activity PKM2 and activates the Wnt pathway to promote the induced expression of HIF-1α by c-MYC and STAT3, thereby increasing the expression of multiple glycolytic related

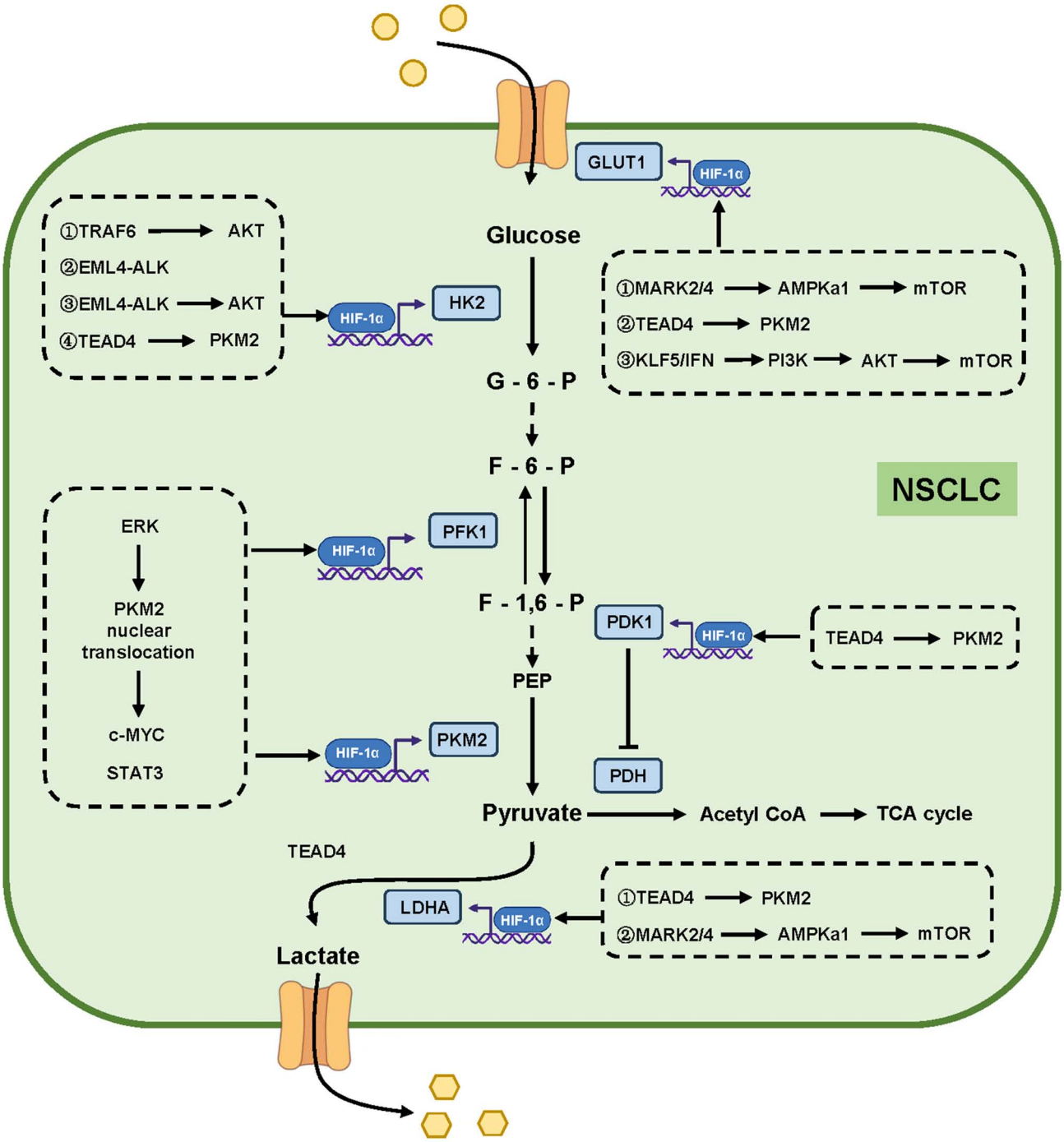

Figure 3. Protein molecules alterations as initiating factors of HIF-1α/glycolysis axis. Activation of different signaling pathways can promote the expression of glycolysis-related enzymes (HK2, PFK1, PKM2, LDHA, GLUT1, and PDK1) by increasing the expression of HIF-1α, and these different pathways work together to promote glycolysis in NSCLC. The activation of different signaling pathways plays a synergistic and complementary role in promoting the expression of all key enzymes of HIF-1α-mediated glycolysis. HIF-1α, hypoxia-inducible factor 1α; NSCLC, non-small cell lung cancer; HK2, hexokinase 2; PFK1, phosphofructokinase; PKM2, pyruvate kinase 2; LDHA, lactate dehydrogenase; GLUT1, glucose transporter 1; PDK1, pyruvate dehydrogenase kinase-1.

enzymes [phosphofructokinase (PFK1), PKM2, pyruvate dehydrogenase kinase 1 (PDK1) and LDHA] (48). Moreover, TEA domain 4 (TEAD4) can act as a transcription factor to promote the transcription of PKM2, which accelerates glycolysis and increases the activity of HIF-1α to increase the expression of GLUT1 and HK2 (49).

Finally, there are mechanisms associated with mTOR, which is the classical molecule that regulates HIF-1α translation. Under the condition of hypoxia in NSCLC, the expression of KLF transcription factor 5 (KLF5) increases to activate the PI3K/AKT/mTOR/HIF-1α pathway, increasing the glucose consumption and lactate production of tumor cells (50). Inflammatory interferon, such as IL-6, promotes the expression of glycolytic related genes by stimulating PI3k/AKT/mTOR to activate HIF-1α (51). At the same time, phosphorylated AMPKa1 can also stimulate mTOR/HIF-1α to increase the expression of GLUT1 and LDHA to promote glycolysis. Microtubule affinity regulating kinase 2/4 is highly expressed

in advanced NSCLC to maintain the phosphorylation level of AMPKa1 and promote tumor cells to glycolysis (52).

The aforementioned studies show that most molecules typically act on HIF-1α ubiquitination and PI3K/AKT/mTOR signaling pathways that alter intracellular HIF-1α content and HIF-1α activity. At the same time, more ncRNAs and protein molecules upstream of HIF-1α in NSCLC tend to regulate HK2, LDHA and PKM2 to alter glycolytic processes. It is evident that blocking HIF-1α for the decreasing of HK2, PKM2 and LDHA transcription has the potential approach to achieve improved therapeutic effects.

4. Progress in targeting the HIF-1α/glycolysis axis for NSCLC treatment

Recent discoveries have elucidated mechanisms by which stable HIF-1α expression in hypoxic environments contributes to drug resistance and treatment ineffectiveness in NSCLC. Novel therapeutic strategies have emerged, focusing on targeting the HIF-1α-mediated hypoxic metabolic characteristics (Table I).

Therapeutic desensitization. Chemotherapy is one of the major ways to treat tumors, but inherent or acquired chemo-resistance limits its clinical application. Platinum-based drugs, central to NSCLC chemotherapy, face resistance mechanisms that are multifaceted, including factors such as platinum transporters, detoxification systems and DNA repair processes (53). These resistance mechanisms are intricately linked to glucose metabolism regulation. It was found that knocking down KLF5 in NSCLC cells alleviated resistance to cisplatin (50). This process is closely linked to the promotion of HIF-1α-dependent glycolysis following deregulation of the KLF5/PI3K/AKT/mTOR pathway activation (50). miR-21 activates the PI3K/AKT/mTOR/HIF-1α pathway, leading to the upregulation of PKM2 and LDHA2 expression. These enzymes are glycolysis-related and are notably abundant in cisplatin-resistant NSCLC cells. Their heightened presence enhances glucose metabolism in tumor cells, contributing to their resistance against cisplatin. Consequently, the elevated expression of miR-21 emerges as a pivotal factor in the development of cisplatin resistance in NSCLC (54). circAKT3 is also a non-coding RNA that is highly expressed in cisplatin-resistant NSCLC. It diminishes the sensitivity of tumor tissue to cisplatin through the regulation of miR-516b-5p/STAT3. However, this effect can be alleviated by suppressing HIF-1α-mediated glycolysis (55). The utilization of etoposide in NSCLC treatment induces elevated intracellular ROS production. This effect activates HIF-1α-mediated metabolic reprogramming, resulting in an upsurge in glycolysis and subsequently leading to increased lactate production. Lactate can regulate the TGF-β1/Snail and TAZ/AP-1 pathways to activate the expression of MRP1/ABCC1 proteins that increase etoposide resistance (56). Scholars have also found that the resistance of NSCLC to paclitaxel is related to the glycolysis promoted by HIF-1α. Evidence suggests that in paclitaxel-resistant tumor cells, glucose uptake relies more on the promotion of GLUT1 expression by pyruvate dehydrogenase kinase 2-activated c-Myc and HIF-1α (57). The increase of HIF-1α-induced glycolysis always promotes the occurrence of drug resistance, which is in line with the current general hypothesis that inhibiting glycolysis can improve chemotherapy (58). However, studies on the relationship between HIF-1α-induced glycolysis and NSCLC resistance to chemotherapeutic agents are fragmented. Further exploration is needed to systematically refine the specific mechanisms involved.

Reduced sensitivity has also been seen in NSCLC radiotherapy. Alternative methods exist to reduce tumor responsiveness to radiation. Particularly, the regulation of the HIF-1α/glycolysis axis has been identified as a promising approach. Researchers have indicated that the stable expression of HIF-1 in NSCLC, achieved through the high expression of miR-210, further prompts cells to manifest mitochondrial defects and glycolytic phenotypes. The existence of this metabolic state is crucial for miR-210 to repair gene double-strand breaks in radiation-resistant NSCLC (59). Cyclocarya paliurus polysaccharide is mainly used to regulate blood glucose and has potential radiosensitization effects when combined with radiotherapy. The specific mechanism is that cyclocarya paliurus polysaccharide inhibits mTOR/AKT/PI3K pathway and reduces HIF-1α expression, which leads to apoptosis of hypoxic NSCLC cells (60). In conclusion, blocking HIF-1α-mediated Warburg effect can effectively enhance the sensitivity of hypoxic tumor tissue to radiotherapy.

EGFR mutants often appear in NSCLC, making EGFR tyrosine kinase inhibitor (TKI)-targeted therapy a prevalent treatment option, though it often encounters resistance issues. In normal cells, SIRT6 acts as a histone H3K9 deacetylase to control the expression of multiple glycolytic genes (61). However, in erlotinib-resistant NSCLC cells, elevated SIRT6 levels enhance glycolysis via the HIF-1α/HK2 axis, reducing the sensitivity of cells to erlotinib. HIF-1α blocker PX478-2HCL blocks this process to alleviate NSCLC resistance to erlotinib (62). Currently, few studies have explored the relationship between the mechanism of EGFR-TKI resistance and the HIF-1α/glycolytic axis. This scarcity might stem from variations in the understanding of tumor metabolic characteristics and their correlation with EGFR-TKI resistance across different academic findings. Some consider that glycolysis promotes EGFR-TKI resistance, while others consider that the metabolic characteristics of drug-resistant tissues tend to be oxidative phosphorylation (63-66).

New treatment options. In recent years, several new NSCLC therapies targeting HIF-1α/glycolysis axis have been discovered (Table I). In hypoxic NSCLC cells, hyperbaric oxygen therapy disrupts the HIF-1α/phosphofructokinase, platelet axis, thus impeding the Warburg effect. This reduction in glycolytic capacity due to the high oxygen concentration effectively inhibits excessive tumor cell proliferation (67). PA-12, an activator of PKM2, can inhibit the nuclear translocation of PKM2 to suppress the expression of HIF-1. Therefore, the glycolysis promoted by HIF-1 is blocked, which affects the proliferation of tumor cells with limited energy supply during hypoxia (68). The HIF-1 inhibitor YC-1 targets the transient activation of LDHA and phosphorylation of the E1a subunit of pyruvate dehydrogenase, effectively inhibiting the metabolic shift from oxidative phosphorylation to glycolysis in tumors. This process impedes the metastatic potential of lung cancer (69). Albendazole is primarily employed as

Table I. Mechanisms of chemotherapy resistance and radiotherapy tolerance associated with HIF-1a/glycolysis.

Author(s), year	Treatment mode	Result or achievement	Mechanism	(Refs.)
Gong *et al*, 2018	Chemotherapy	Resistance to cisplatin	KLF5 → PI3K/AKT/mTOR→ HIF-1a/ glycolysis → resistance	(50)
Sun *et al*, 2021			miRNA-21 → PI3K/AKT/mTOR pathway → HIF-1a/glycolysis → resistance	(54)
Xu *et al*, 2020			circAKT3 → miR-516b-5p/STAT3 → resistance (inhibition of HIF-1a/ glycolysis can attenuate this effect)	(55)
Dong *et al*, 2020		Resistance to etoposide	Etoposide→ ROS → HIF-1a/glycolysis → Lactic acid → TGF-β1/Snail and TAZ/AP-1 pathway → MRP1/ABCC1 proteins → resistance	(56)
Sun *et al*, 2017		Resistance to paclitaxel	Glucose uptake in paclitaxel resistant tumor cells is more dependent on the promotion of GLUT1 expression by PDK2 activated c-Myc and HIF-1a	(57)
Grosso *et al*, 2013	Radiotherapy	Low sensitivity to radiotherapy	miR-210 → HIF-1a/glycolysis → low sensitivity	(59)
Zhang *et al*, 2019		Enhance sensitivity	Cyclocarya paliurus polysaccharide inhibits mTOR/AKT/PI3K pathway →HIF-1a↓ → apoptosis of hypoxic cells → sensitivity enhanced	(60)
You *et al*, 2022	TKI	Resistance to erlotinib	SIRT6 → HIF-1a/HK2 → resistance	(62)
Zhang *et al*, 2021	New methods to treat tumor through metabolic pathway (Reduce the energy source of tumor cells)	Hyperbaric oxygen therapy	Inhibit HIF-1a/PFKP axis	(67)
Kim *et al*, 2015		PA-12	PA-12 → Inhibit nuclear translocation of PKM2 → HIF-1a/glycolysis→	(68)
Zhao *et al*, 2014		YC-1	YC-1 → HIF-1↓→ The activity of LDHA and pyruvate dehydrogenase was downregulated → glycolysis→	(69)
Zhou *et al*, 2017.		Albendazole	Albendazole → HIF-1a↓ → glycolysis→	(70)
Yang *et al*, 2021		Deoxypodophyllotoxin	Deoxypodophyllotoxin→ parkin mediated protein degradation→ HIF-1a↓ → GLUT1/HK2/LDHA→	(71)
Liu *et al*, 2021		Huaier	Huaier→ inhibit PI3K/AKT/HIF-1a signaling pathway → glycolysis/glucose uptake↓	(72)
Huang *et al*, 2022		Nanoparticle	Deliver EGFR-TKI and YAP-siRNA → HIF-1a↓ → Glycolysis↓	(75)
Alkhathami *et al*, 2023			Deliver circRNA→ HIF-1a↓→Glycolysis↓	(76)
Kopecka *et al*, 2015			Deliver Zoledronic acid→ inhibit Ras/erk1/2→ activation of HIF-1a ↓→glycolysis↓	(53)

HIF-1α, hypoxia-inducible factor 1α; PFKP, phosphofructokinase, platelet; KLF5, KLF transcription factor 5; miR, microRNA; circRNA, circular RNA; ROS, reactive oxygen species; GLUT1, glucose transporter 1; PDK1, pyruvate dehydrogenase kinase 1; LDHA, lactate dehydrogenase; PKM2, pyruvate kinase 2; PDH, pyruvate dehydrogenase.

an anthelmintic and insect repellent (70). However, recent research has revealed its additional potential. Albendazole has been shown to downregulate the expression of HIF-1α and decrease the levels of HK, PK and LDH in tumor cells under hypoxic conditions. This mechanism inhibits glycolysis in NSCLC, ultimately impeding their proliferation (70). Deoxypodophyllotoxin hinders NSCLC progression through a two-fold mechanism. Initially, it disrupts angiogenesis in the tumor vicinity. Second, it facilitates parkin-mediated protein degradation, resulting in decreased expression of HIF-1α and subsequently reducing the levels of HIF-1α target genes such as GLUT1, HK2, and LDHA (71). The Chinese medicine Huaier is currently an adjunct drug in the treatment of a number of cancers. It can inactivate PI3K/AKT/HIF-1α pathway, downregulate glycolysis and glucose transport in NSCLC and exert anti-tumor effects (72). For squamous NSCLC, Fibroblast Growth Factor Receptor 1 (FGFR1) is often overexpressed. Targeting FGFR1 may prevent cancer cell growth by inhibiting glucose metabolism, as FGFR1 activates the AKT/mTOR pathway for HIF-1α accumulation and thus increases glucose uptake and glycolysis (73).

In addition, nanoparticles are gaining traction in tumor medicine, with ongoing clinical translation efforts (74). A newly invented nanodrug can simultaneously target the delivery of EGFR-TKI and yes associated protein (YAP)-siRNA combination drugs, addressing the role of YAP in epidermal growth factor receptor-TKI resistance in NSCLC. This nanodrug diminishes the glycolysis function by downregulating HIF-1α, enhancing tumor cell sensitivity to photodynamic therapy-induced apoptosis (75). Nanoparticles can be utilized to deliver circRNAs for the treatment of NSCLC. These circRNAs, either directly or through the inhibition of glycolysis via HIF-1α, hold promise as a therapeutic approach for NSCLC (76). Zoledronic acid-loaded nanoparticles suppress isoprenoid synthesis and HIF-1α activation through the Ras/erk1/2 pathway, decreasing glucose transport and glycolytic enzyme transcriptional activity. This method shows promise in combating multidrug-resistant tumors (53).

5. Conclusions

HIF is an important metabolic regulatory molecule in tumors and the dysregulation of HIF expression is necessary for tumor survival and growth (77). The expression of HIF-1α mainly affects the balance between glycolysis and oxidized phosphoric acid in higher metazoan tumor cells. However, there is no universal mechanism for reprogramming glucose metabolism in all cancers (58), so the present review focused on NSCLC. The present review summarized the regulatory mechanism of HIF-1α/glycolysis in order to discover the regulatory characteristics of glucose metabolism in NSCLC and paved the way for finding the mechanism that is common in different cancers. It characterized the regulatory mechanisms of HIF-1α in NSCLC according to different stages affecting HIF-1α expression, reflecting the unique regulatory pattern of HIF-1α in NSCLC. Part of the mechanism can be reflected in the mechanism of the regulation of HIF-1α-mediated glycolysis. For example, the inflammatory factor IL-6 can increase the expression of HIF-1α through STAT3 and promote glycolysis (29). The section 'Regulatory mechanism of HIF-1α/glycolysis axis in NSCLC' summarized the types of regulatory molecules and classical pathways as clues. It was found that ncRNA and PI3K/AKT/mTOR signaling pathways play an important role in regulating the HIF-1α/glycolysis axis, and most of them regulate the glycolysis process by affecting the downstream HK2 content. In addition, it was found that the accumulation of HIF-1α and the overexpression of HIF-1α promote glycolysis to form a cycle promoting a mutually stable relationship. Taking the regulatory mechanism in NSCLC as an example, HIF-1α can promote the expression of PKM2 to accelerate glycolysis. At the same time, low PKM2 activity leads to decreased glycolysis but can induce HIF-1α expression to solve this conundrum.

The mechanism of glucose metabolism reprogramming is gradually being analyzed, and it is generally considered that the regulation of glucose metabolism may be one of the important development directions for cancer treatment in the future (78). A variety of NSCLC treatment modalities and resistance mechanisms related to the HIF-1α/glycolysis axis were summarized in part three of the present review. The central idea behind these approaches is to alter the specific metabolic pattern of tumors by blocking HIF-1α expression and activation or disabling glycolytic rate-limiting enzyme to aid classical NSCLC therapy. However, in the case of tumor development led by HIF-1α/glycolysis, a more ideal therapeutic target is that of selective intervention of HIF-1 pathway (79). Selectivity can be manifested in the development of inhibitors that target molecules that regulate HIF-1α to initiate the transcription process of glycolytic enzymes, rather than HIF-1α or glycolytic rate-limiting enzymes or upstream molecules that regulate HIF-1α themselves. This allows for more precise regulation of HIF-1α-mediated changes in tumor metabolism without affecting other roles of HIF-1α and other molecules in complex signaling pathway networks. There are few relevant studies on HIF-1α initiating the transcription of glycolysis-related genes in NSCLC (46). If more targets that selectively inhibit this axis can be found in the future, it will promote the research of methods to treat NSCLC by regulating metabolism.

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Authors' contributions

YS and GC conceived and designed the article. YS and XL surveyed the literature and wrote the manuscript. JW, ZZ and SC surveyed the literature and provided suggestions. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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