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Review article

PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism: Potential targets to overcome radioresistance in small cell lung cancer

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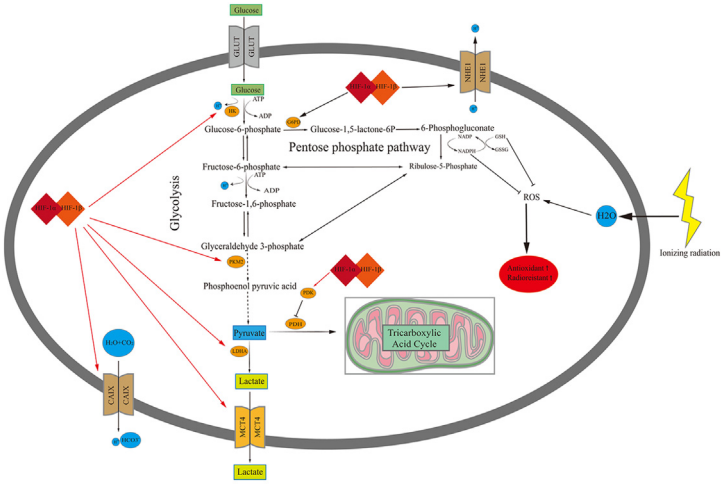
HIGHLIGHTS

- The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway was frequently activated in small cell lung cancer (SCLC) and was closely associated with radioresistance.
- This pathway can be involved in regulating glucose metabolism, which can affect radioresistance by influencing energy metabolism.
- The interaction between the PI3K/AKT/mTOR pathway and glucose metabolism was primarily mediated by hypoxia-inducible factor 1 (HIF-1) signaling, and this pathway may also affect glucose metabolism through other mechanisms, including inhibition of the ubiquitinated degradation of the rate-limiting enzyme of the pentose phosphate pathway (G6PD).

GRAPHICAL ABSTRACT



Mechanisms underlying aerobic glycolysis, oxidative phosphorylation, and pentose phosphate pathway regulation by hypoxia-inducible factor 1 in radioresistance.

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ABSTRACT

Small cell lung cancer (SCLC) is a highly aggressive tumor type for which limited therapeutic progress has been made. Platinum-based chemotherapy with or without thoracic radiotherapy remains the backbone of treatment, but most patients with SCLC acquire therapeutic resistance. Given the need for more effective therapies, better elucidation of the molecular pathogenesis of SCLC is imperative. The phosphoinositide 3-kinase (PI3K)/protein

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Glucose metabolism
Radioresistance

kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is frequently activated in SCLC and strongly associated with resistance to ionizing radiation in many solid tumors. This pathway is an important regulator of cancer cell glucose metabolism, and its activation probably effects radioresistance by influencing bioenergetic processes in SCLC. Glucose metabolism has three main branches—aerobic glycolysis, oxidative phosphorylation, and the pentose phosphate pathway—involved in radioresistance. The interaction between the PI3K/AKT/mTOR pathway and glucose metabolism is largely mediated by hypoxia-inducible factor 1 (HIF-1) signaling. The PI3K/AKT/mTOR pathway also influences glucose metabolism through other mechanisms to participate in radioresistance, including inhibiting the ubiquitination of rate-limiting enzymes of the pentose phosphate pathway. This review summarizes our understanding of links among the PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism in SCLC radioresistance and highlights promising research directions to promote cancer cell death and improve the clinical outcome of patients with this devastating disease.

Introduction

Lung carcinoma is a serious public health problem globally with high morbidity and mortality, giving rise to high socio-economic pressure.[1] Small cell lung cancer (SCLC) accounts for about 15% of lung cancers and has the highest-grade malignancy among all subtypes of lung cancer.[2] SCLC can be either limited-stage (LS-SCLC) or extensive-stage (ES-SCLC). Concurrent chemoradiotherapy (CCRT) remains the standard of care for LS-SCLC.[2,3] Despite the high initial response rate to chemotherapy and radiotherapy, therapeutic resistance almost always occurs in SCLC, followed by recurrence or disease progression.[2,4] The resistance of SCLC to radiotherapy remains an important challenge given the low 5-year survival rate in patients with this devastating disease.[5] Given the requirement for more effective therapies, delineation of the molecular pathogenesis of SCLC is imperative.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling is activated following ionizing radiation, which increases cancer cell survival. This pathway was also found to be activated in patients with relapsed SCLC who previously received CCRT compared with that in treatment-naïve patients.[6] Furthermore, the PI3K/AKT/mTOR pathway regulates hypoxia-inducible factor 1 (HIF-1)α expression through phosphorylation of two downstream effectors: ribosomal protein S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E (eIF-4E)-binding protein 1 (4E-BP1).[7,8] mTOR contains two structurally different multiprotein complexes—mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2)—which promote aerobic glycolysis, glutaminolysis, and the pentose phosphate pathway (PPP) by regulating the expression and activity of transcription factors such as HIF-1α and myelocytomatosis oncogene (*MYC*) and either activating or inactivating metabolic enzymes (such as glucose transporters, hexokinase, and glutamine synthetase).[9–11]

Hypoxia frequently occurs in solid tumors and can prevent fixation of DNA damage by oxygen, believed to be the mechanism underlying radioresistance.[12] In addition, the hypoxic microenvironment can activate the HIF-1 pathway, which helps cancer cells avoid death via upregulation of their glucose uptake and utilization.[13,14] Hypoxia is also involved in cancer cell proliferation, angiogenesis, metastasis, and pH regulation, which can coordinate to reduce the efficacy of radiation treatment, eventually leading to cancer relapse.[14]

Cancer cells preferentially utilize glycolysis even in the presence of oxygen, producing large quantities of lactic acid as the metabolic byproduct, known as the Warburg effect. High glycolytic states of cancers significantly correlate with radiation resistance and aggressive biological behavior.[15,16] The Warburg effect is involved in resistance to radiotherapy and/or chemotherapy.[17] The PPP is another branch of glucose metabolism, and tumor cells upregulate the PPP to produce reductive metabolites and detoxify chemoradiotherapy-induced reactive oxygens species (ROS).[18,19] Therefore, targeting the glucose metabolism of tumor cells is a potential therapeutic approach for improving the efficacy of radiation therapy.

In this review, we summarize and discuss how the PI3K/AKT/mTOR and HIF-1 pathways influence SCLC radioresistance by modifying glucose metabolism in cancer cells. We also discuss suppression of the PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism as a potential therapeutic strategy to overcome this radioresistance.

Radioresistance of SCLC cells

CCRT remains the standard first-line treatment for LS-SCLC, and thoracic radiotherapy can improve the local control rate, reduce recurrence risk, and prolong survival for patients with ES-SCLC.[20,21] Direct and indirect effects can be induced by applying ionizing radiation especially in rapidly proliferating tumor cells. The former refers to direct interactions between particles and relevant macromolecules, whereby the damage can usually be repaired. The latter plays a dominant role in biological damage, which leads to interactions between water and oxygen molecules near and inside tumor cells. Subsequently, ROS, including superoxide and hydroxyl radicals, are produced. These accumulate to cause irreversible damage to DNA and other macromolecules in tumor cells and provoke apoptosis by inducing cellular stress response and activating the intrinsic apoptosis cascade.[22,23] Although an initial high sensitivity to chemotherapy and radiotherapy is observed, treatment resistance almost always develops in patients with SCLC. Resistance to radiation is a complex phenomenon that requires further elucidation; nonetheless, two potential explanations can be given. First, the surviving cancer cells were forced to adapt and acquire resistance under the multiple exposures of ionizing radiation. Second, cancer cells with high radiosensitivity are killed by radiation, but those with low radiosensitivity survive, proliferate rapidly, and become predominant. Preclinical and clinical studies have revealed some potential mechanisms underlying radioresistance, including alteration of DNA repair capacity, gene expression regulation, cell cycle arrest, autophagy induction, cancer cell glucose metabolism reprogramming, and cancer stem cell activity.[24–26]

Role of the PI3K/AKT/mTOR pathway, hypoxia, glucose metabolism, and radiotherapy in SCLC radioresistance

PI3K/AKT/mTOR pathway in SCLC

The PI3K/AKT/mTOR signaling pathway is essential to the cell cycle, cell growth, cell survival, glucose metabolism, and protein synthesis [Figure 1]. This pathway is frequently altered across various malignancies, including SCLC, breast cancer, and ovarian cancer. PI3Ks belong to the intercellular lipid kinase family, which phosphorylates the 3′-OH functional group of phosphatidylinositol. PI3Ks have three different subtypes, subtype 1 being the most important, as it can transform phosphatidylinositol biphosphate (PIP2) into phosphatidylinositol triphosphate (PIP3). As a secondary messenger, PIP3 recruits and activates kinases with the pleckstrin homology domain, such as PI3K-dependent kinase 1 (PDK1). Phosphatase and tensin homology (*PTEN*) is a tumor-suppressor gene that dephosphorylates PIP3 and is an important negative regulator of the PI3K/AKT/mTOR pathway.[2728] *PTEN* mutation or deletion frequently occurs in malignancies, and its epigenetic silencing has been reported to induce overactivation of the PI3K/AKT/mTOR pathway in various cancers.[28]

As a downstream kinase of PI3K, AKT is completely activated when its T308 and S473 residues are phosphorylated by mTORC2 and PDK1. This then causes phosphorylation of enzymes such as glycogen synthase kinase 3 beta (GSK3β), hexokinase 2 (HK2), murine double minute 2 proto-oncogene (MDM2), tuberous sclerosis 2 (TSC2), B-cell chronic

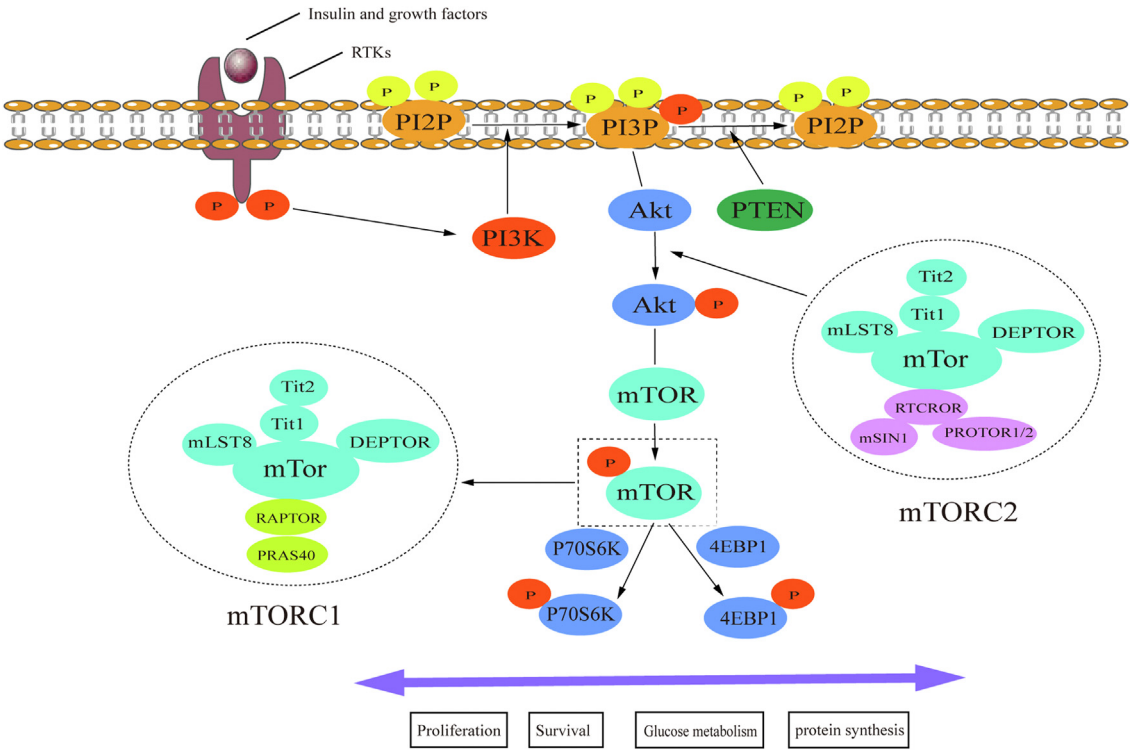

Figure 1. The PI3K/AKT/mTOR pathway. Insulin or growth factors trigger PI3K activation, which causes PIP2 phosphorylation and PIP3 production. PTEN antagonizes the kinase activity of PI3K by dephosphorylating PIP3. As a phosphate source, PIP3 transfers a phosphate group to AKT and activates it. AKT contains different regulatory sites that can be phosphorylated by mTORC2. As a kinase, AKT phosphorylates downstream targets such as mTORC1, which eventually regulates cell proliferation, survival, glucose metabolism, and protein synthesis through p70S6K and 4EBP1 phosphorylation. PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; PIP2: Phosphatidylinositol-4,5-bisphosphate; PIP3: Phosphatidylinositol-3,4,5-trisphosphate; mTORC: mTOR complex.

lymphocytic leukemia/lymphoma 2 (BCL2) associated agonist of cell death (BAD), mTOR, and HIF-1.[29,30] AKT is involved in a wide range of cellular processes, including glucose metabolism and cell proliferation and survival. mTOR is a downstream kinase of the PI3K/AKT pathway and contains two kinds of multiprotein complexes: mTORC1 and mTORC2 [Figure 1].

mTORC1 is a rapamycin- and nutrient-sensitive complex that plays an important role in cell growth, proliferation, and survival by regulating the expression of many proteins via mTORC1-induced phosphorylation of p70S6K and 4EBP1.[30] Phospho-mTOR (a marker of mTOR kinase activity) and phospho-p70S6K (a downstream target of mTORC1) is present in 55% and 91% of SCLC tumors, respectively.[31,32] Through immunohistochemical analysis, 66% of SCLC tissues were found to be positive for phospho-4EBP1 (another downstream target of mTORC1), and non-smoking patients and those with metastasis were found to have higher positivity rates for p-4EBP1. In addition, patients with higher levels of p-4EBP1 had less favorable survival ($P = 0.016$).[33]

mTORC2 regulates cytoskeletal organization and is insensitive to rapamycin. This complex also indirectly affects glucose metabolism and cell proliferation and survival by phosphorylating and activating AKT.[30] Rapamycin-insensitive companion of mTOR (*RICTOR*), encoding a scaffold protein of mTORC2, was found to be the most frequently amplified gene in 10%–15% of patients with SCLC, using next-generation sequencing or fluorescence *in situ* hybridization.[31,34] Furthermore, the copy number variation of *RICTOR* was correlated with its protein expression level in SCLC cell lines.[35] The positivity rate for *RICTOR* and phospho-AKT (a downstream kinase of mTORC2) was found to be 37% and 42%, respectively, using immunohistochemical analysis.[31] Chemotaxis and scratch wound assays also revealed that SCLC cell lines with *RICTOR* amplification could migrate more quickly and were more susceptible to mTOR inhibitors. Furthermore, patients with *RICTOR* amplification had considerably worse survival than those without ($P = 0.021$).[35]

Genomic profiling studies have greatly improved our understanding of the molecular characteristics of SCLC.[34,36,37] Comprehensive genomic studies have revealed that 7%–36% of SCLC tumors harbor *PTEN, PIK3CA, AKT2, AKT3, RICTOR,* and *MTOR* mutations.[37,38] In a bioinformatic analysis of 130 blood samples from patients with ES-SCLC, those harboring PI3K/AKT/mTOR alterations were associated with a higher blood tumor mutational burden.[39] A recent study found that PI3K/AKT/mTOR pathway activation contributes to phenotypic switching from suspension to adhesion or semi-adhesion growth pattern and confers SCLC cells with resistance to chemotherapy.[40] microRNA (miRNA, miR) polymorphisms in the PI3K/AKT/mTOR pathway are important prognostic factors among patients with LS-SCLC, and three single-nucleotide polymorphisms—MTOR: rs2536 (T > C), PIK3R1: rs3756668 (A > G), and PIK3R1: rs12755 (A > C)—are correlated with favorable prognosis.[41]

Role of the PI3K/AKT/mTOR pathway in radioresistance

Understanding the mechanisms underlying radioresistance is relevant for exploring new therapeutic strategies. With the rapid development of advanced analytical methods, including genomics and proteomics, progress has been made in the exploration of radioresistance-associated signaling pathways. The effects of activating the PI3K/AKT/mTOR pathway on radioresistance have been extensively studied. miR-410 contributes to epithelial-mesenchymal transition (EMT) and resistance to ionizing radiation by activating PI3K/AKT/mTOR signaling in non-SCLC (NSCLC) both *in vitro* and *in vivo*.[42] Through label-free quantitative liquid-chromatography/tandem-mass spectrometry, this pathway was found to be the most activated pathway correlated with radioresistance in three prostate cancer cell lines resistant to ionizing radiation.[43] A recent study that compared paired SCLC samples from 11 patients with LS-SCLC at diagnosis and relapse using genomic analyses

demonstrated that genes belonging to the PI3K/AKT signaling pathway were significantly enriched in the relapse samples.[6]

The PI3K/AKT/mTOR pathway may induce resistance to ionizing radiation in tumor cells via neoangiogenesis, cell cycle, DNA repair, and hypoxia. Ionizing radiation causes reoxygenation and neoangiogenesis in tumor cells, and this is partially due to vascular endothelial growth factor (VEGF) upregulation through HIF-1α activation regulated by the PI3K/AKT/mTOR pathway. Then, VEGF preserves endothelial cells against radiation-induced damage by activating the PI3K/AKT/mTOR pathway, causing upregulation of anti-apoptotic proteins, including Bcl2.[44] Anti-angiogenesis could cause vasculature normalization, enhancing perfusion and alleviating hypoxia, thus improving the cytotoxic effects of radiation. Some compounds, including PI3K/AKT inhibitors, can disrupt the vasculature through direct or indirect inhibition of VEGF. A combination of low-dose LY294002 (PI3K inhibitor) and cisplatin considerably improved the efficacy of radiotherapy by decreasing neovascularization.[45] Ionizing radiation can lead to p53-dependent or p53-independent G1 and G2 arrest of the cell cycle, but the PI3K/AKT/mTOR pathway overrides the p53-independent cell cycle arrest by activating cyclin D and inactivating the cell cycle-dependent kinase inhibitor p27.[46] DNA damage repair depends on three important kinases—DNA-dependent protein kinase catalytic subunit (DNA-PKcs), ataxia-telangiectasia mutated (ATM), and ATM- and RAD3-related proteins—and the dual PI3K/mTOR inhibitor NVP-BEZ235 can potently inhibit ATM- and DNA-PKC-mediated DNA double-strand break repair, increase DNA damage in cancer cells, and enhance the cytotoxic effect of radiotherapy.[47,48]

Hypoxia in SCLC

Hypoxia, involving low oxygenation levels, is one of the most important hallmarks of cancer; oxygen levels in cancer are <2%, whereas normal oxygen concentration is 3.2–12.3%. Hypoxia is mainly caused by the rapid proliferation and dysfunctional vascularization of and consumption of available oxygen in tumor cells.[49] The HIF-1 pathway is activated in cancer cells exposed to a hypoxic microenvironment. HIF-1 is an important transcription factor consisting of HIF-1α and HIF-1β. HIF-1β shows constitutive expression, but the expression and function of HIF-1α are largely controlled by the oxygen level. Under low oxygen concentrations, HIF-1α avoids degradation and accumulates to help cancer cells resist the temporary stress. Activation of HIF-1 signaling can upregulate the transcription of many genes in glucose metabolism, such as those encoding glucose transporters (GLUTs), glycolytic enzymes, and carbonic anhydrases. Regulation of these genes in tumor cells leads to metabolic conversion from aerobic respiration to glycolysis and utilization of the PPP. Although not all cancer cells are exposed to hypoxia, the adaptive response to hypoxia confers more aggressive and therapy-resistance properties to cancer cells.[50,51]

Patients with SCLC frequently experience breathing difficulty due to obstruction by tumors, pleural effusion, chronic obstructive pulmonary disease, and tar from cigarettes, causing insufficient oxygenation in blood and tissues. Additionally, chemotherapy often induces anemia in patients, decreasing their ability to transport oxygen in the blood.[52] Histological analysis of biopsy samples has shown hypoxic regions in more than 50% of patients newly diagnosed with SCLC, and this value may be higher when considering the small size of samples analyzed and the failure to reveal full intra-tumor heterogeneity.[53] The presence of hypoxic regions in SCLC is strongly associated with tumor progression and unfavorable survival, and HIF-1α is an independent prognostic factor ($P < 0.003$) among patients with SCLC, even after adjusting for clinical parameters.[54] Moreover, HIF-2α is correlated with shorter survival in patients with SCLC,[55] so both HIF-1α and HIF-2α are attractive molecular targets in SCLC.

Role of hypoxia in radioresistance

Ionizing radiation kills tumor cells primarily by inducing ROS production under oxygenated conditions. In hypoxic cells, ROS formation is limited, DNA damage can be repaired, and death can be avoided.[56] Therefore, tumor cells in a well-oxygenated environment are far more sensitive to ionizing radiation than hypoxic cells. To measure this phenomenon, the oxygen enhancement ratio, which is the ratio of radiation doses delivered under hypoxia to normal oxygen concentration required to achieve the same biological end-points, can be utilized. In fact, radiation doses in hypoxic cells are evidently higher than those in normoxic cells to reach the same mortality rate. Tumor cells in a hypoxic environment are two to three times more resistant to ionizing radiation than those in a normoxic environment.[49,57] The concentration of and duration of exposure to oxygen are important factors in this regard. To achieve efficient cytotoxicity, an adequate molecular oxygen level is required during radiation therapy or at least during the lifetime of the ROS induced by ionizing radiation.

Moreover, the cell cycle affects sensitivity to radiation, and hypoxia can influence cell cycle progression, during which the radioresistance of tumor cells is dynamically altered. Cancer cells in the G2-M phase are most sensitive to radiotherapy, those in the G1 phase are less radiosensitive, and those in the S phase are least radiosensitive.[58] Under hypoxic conditions, S-phase entry is hindered by HIF-1α through its regulation of genes encoding proteins in cell cycle regulation. p21 and p27, important cyclin-dependent kinase inhibitors, are significantly upregulated under hypoxia, leading to cell cycle arrest and reduced radiotherapy efficacy.[59]

Role of glucose metabolism in SCLC

To meet their energy and biosynthetic demands, cancer cells prefer glycolysis over oxidative phosphorylation (OXPHOS), even in the presence of oxygen. Using fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), the significant increase in glucose uptake by cancer cells has been used to evaluate therapy response and diagnose SCLC, particularly LS-SCLC.[60,61] According to FDG-PET/CT results, maximum or integrated standardized values of glucose uptake, metabolic tumor volume, and total lesion glycolysis are negatively associated with the prognosis of patients with SCLC.[62] Glucose metabolism promotes cell proliferation and growth by rapidly producing energy, generating intermediate products used to synthesize nucleotides, amino acids, and lipids, and maintaining redox homeostasis.[63] The major source of nicotinamide adenine dinucleotide phosphate (NADPH) in the cytoplasm is the PPP, which is required to scavenge cellular ROS and eventually enhance the antioxidant capacity of tumor cells [Figure 2].[18,19] Hence, glucose metabolism, mainly comprising glycolysis, the PPP, and the citric acid cycle, shows potential and is attracting growing attention as a therapeutic target in SCLC.

Elevated glucose uptake and lactate production are crucial hallmarks of glucose metabolism in cancer cells. Specific genetic alterations can cause metabolic liabilities in tumors. Overexpression of genes with oncogenic functions, including *c-MYC*, *RAS*, *PI3K,* and *AKT*, increases glucose uptake and upregulates transporters or enzymes involved in aerobic glycolysis and/or the PPP.[64] Conversely, p53 serves as a tumor suppressor by inhibiting glycolysis or the PPP and promoting OXPHOS.[65] *TP53* is either deleted or mutated across various tumors, including SCLC. According to comprehensive genomic profiling, 90% of SCLC cases lack functional p53,[66] so its regulation of glucose metabolism is mostly lacking. Moreover, amplification or overexpression of *MYC* and other genetic alterations leading to overactivation of the PI3K/AKT/mTOR pathway are frequently observed in patients with SCLC. Thus, a large proportion of SCLC tumors exhibit high states of glycolysis and/or PPP.

A recent study divided SCLC cells into two groups—MYC^{High} and MYC^{Low}—and explored the differences between glycolysis and OXPHOS both *in vitro* and *in vivo*.[67] The MYC^{High} group was sensitive to glycolysis inhibition, whereas the MYC^{Low} group remained primarily unresponsive, suggesting that *MYC* defined the predominant metabolic phenotype. Hence, it was concluded that SCLC tumors with high *MYC* expression strongly depend on glycolysis, whereas those with either low or no *MYC* expression mainly exhibit the OXPHOS phenotype. In addition,

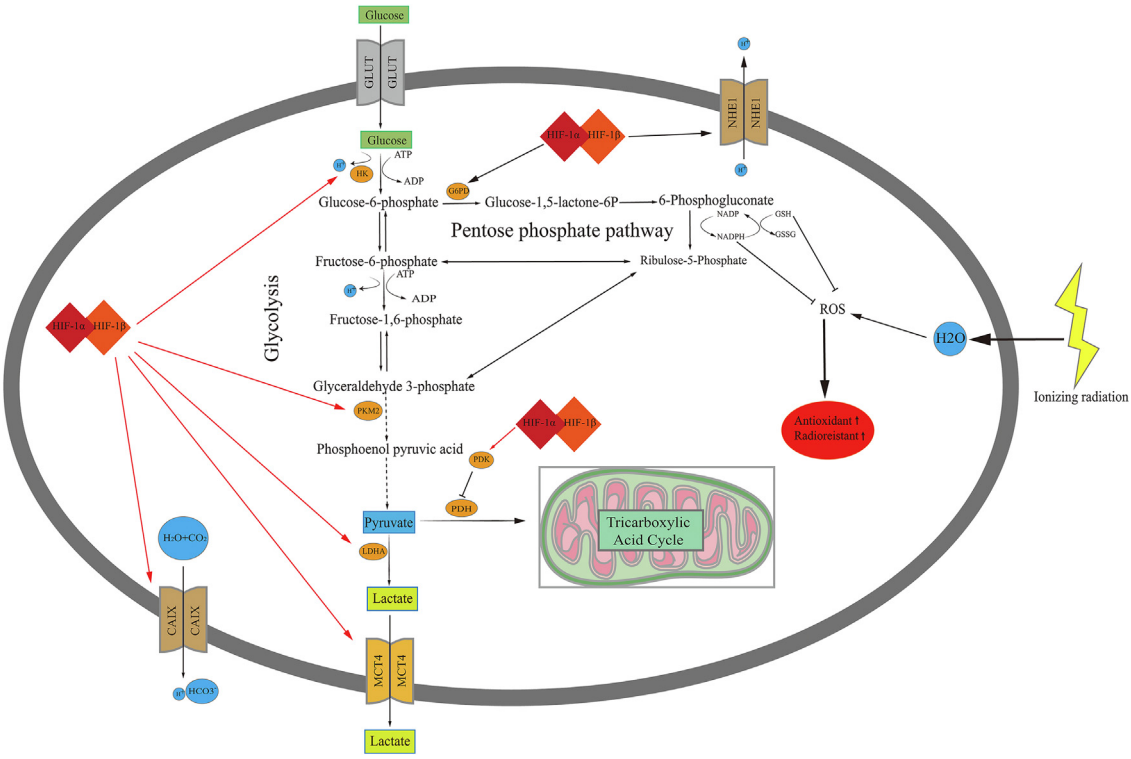

Figure 2. Mechanisms underlying aerobic glycolysis, OXPHOS, and PPP regulation by HIF-1 in radioresistance. ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; CAIX: Carbonic anhydrase 9; G6PD: Glucose-6-phosphate dehydrogenase; GLUT: Glucose transporters; GSH: Glutathione; GSSG: Glutathione disulfide; HIF-1: Hypoxia-inducible factor-1; HK: Hexokinase; LDHA: Lactate dehydrogenase A; MCT4: Monocarboxylate transporter 4; NHE1: Naþ/Hþ exchanger isoform 1; OXPHOS: Oxidative phosphorylation; PDH: Pyruvate dehydrogenase; PDK: Pyruvate dehydrogenase kinase; PPP: Pentose phosphate pathway; ROS: Reactive oxygen species.

correlations between metabolites and prognosis in SCLC cases have been reported. A retrospective analysis of 98 patients with SCLC who underwent pretreatment FDG-PET/CT revealed that increased levels of serum lactate dehydrogenase (LDH), which catalyzes the final stage of aerobic glycolysis, were associated with overall survival (OS) (hazard ratio [HR] = 1.8, 95% confidence interval [CI]: 1.16–2.77, P = 0.008) and progression-free survival (HR = 1.71, 95% CI: 1.11–2.64, P = 0.015).[68] Recently, a similar study on 234 patients with SCLC also demonstrated the independent prognostic value of LDH and reported patients with pretreatment LDH ≥215.70 U/L to have significantly unfavorable survival (HR = 1.468, 95% CI: 1.069–2.017, P = 0.018).[69] In another study, pretreatment LDH level was negatively correlated with relapse-free survival (HR = 2.8, 95% CI: 1.03–7.52, P = 0.043), but LDH level and glucose transporter 1 (*GLUT-1*) were associated with a higher objective response rate (ORR) among 41 patients with SCLC who underwent CCRT.[70]

Role of glucose metabolism in radioresistance

Emerging evidence has revealed that tumor cells in which glycolysis activity and/or the PPP are significantly upregulated are less sensitive to radiotherapy and have more aggressive phenotypes. Irradiation-induced ROS not only damages cancer cell DNA but also elevates the glucose uptake by tumor cells during reoxygenation; a kind of antioxidant superoxide dismutase (SOD) mimic was found to evidently reduce the glucose uptake induced by irradiation and suppress the glycolytic switch.[71] Tyrosine phosphorylation caused by the SRC proto-oncogene, non-receptor tyrosine kinase (SRC) family kinase Fyn was shown to increase 6-phosphogluconate dehydrogenase activity in glioma by enhancing its binding affinity to $NADP^+$ and activating the PPP to produce NADPH and ribose-5-phosphate, which detoxify intracellular ROS and promote DNA synthesis, finally leading to glioma cell proliferation and radioresistance.[18] To explore clinically relevant radioresistance, many radioresistant cell models have been established, and cancer cells are frequently exposed to x-rays 15–30 times (sustained irradiation) to induce radioresistance. Radioresistant head and neck squamous cells presented significantly different metabolic alterations in which glucose uptake and fatty acid biosynthesis were enhanced, the PPP was upregulated, and OXPHOS was downregulated.[72] Moreover, radioresistant glioblastoma multiforme (GBM) cells showed a higher glycolytic state and increased stemness through the Spy1-(CAP-Gly Domain Containing Linker Protein 3)CLIP3 axis, and rescuing CLIP3 expression was shown to be a potential approach for reversing GBM radioresistance.[26]

A recent study using proteomic, metabolomic, and metabolic flux analyses suggested that compared with their parental cells, radioresistant hepatocellular carcinoma cells exhibited elevated glucose flux and higher mRNA levels of genes involved in glycolysis, including *HK2* and *GLUT-1*, causing cardiolipin upregulation, which reduces the efficacy of irradiation by suppressing the release of cytochrome C to activate the apoptosis cascade.[13] miR-223-3p was reported to contribute to radioresistance in prostate cancer by increasing glycolysis via targeting Forkhead Box O3 (FOXO3a).[73] Patients with oral squamous cell carcinoma with higher *GLUT-1* expression were less responsive to preoperative radiation therapy at 36 Gy than those with lower *GLUT-1* expression (P = 0.005).[74]

To the best of our knowledge, no study related to SCLC cells with secondary radioresistance has been published yet. CPH 54A and CPH 54B are distinct SCLC cell subpopulations established from the same patient. Despite their common genomic origin, the cell lines exhibit distinct phenotypes.[75] CPH 54B has stronger radioresistance than CPH 54A both *in vivo* and *in vitro*. Furthermore, CPH 54B tumors have lower oxygen consumption, steady-state adenosine triphosphate (ATP) levels, cellular ATP concentrations, and higher lactate production than CPH 54A tumors.

Interestingly, CPH 54B tumors have higher mRNA and protein levels of *GLUT-1* and correspondingly higher FDG uptake both *in vitro* and *in vivo*, suggesting the glycolytic predominance of CPH 54B.[76]

The PI3K/AKT/mTOR pathway and hypoxia

PI3K activation upregulates HIF-1α protein expression and plays an important role in regulating protein synthesis through its target AKT and downstream component mTOR. eIF-4E is the mRNA 5′ cap-binding protein that participates in the translation of many proteins. The family of repressor proteins, 4E-binding proteins (4E-BPs), control eIF-4E activity, and the phosphorylation status of 4E-BPs determine whether they bind to eIF-4E. On the one hand, mTOR mediates its action by phosphorylating 4E-BP1, after which 4EBP1 is released from eIF-4E, leading to the failure of inhibiting cap-dependent mRNA translation and initiation of cap-dependent translation.[77,78] On the other hand, mTOR causes the phosphorylation of p70S6K and then phosphorylates its substrate, the ribosomal protein S6, inducing the translation of many proteins [Figure 1].[78] Based on the understanding of these mechanisms, it was concluded that HIF-1 translation could be greatly increased in tumor cells by activating the PI3K/AKT/mTOR pathway.

Wan et al. revealed that HIF-1α promoted proliferation and angiogenesis of residual SCLC (NCI–H446 cell line) and NSCLC (NCI–H1650 cell line) cells following hyperthermia treatment. In NSCLC, HIF-1α expression was shown to be controlled by both the PI3K/AKT and extracellular signal-regulated kinase (ERK) pathways, whereas, in SCLC, HIF-1α levels were reported to be controlled by only the PI3K/AKT pathway.[79] The suppressor of cytokine signaling 3 (SOCS3) was reported to target the PI3K/AKT pathway to block HIF-1α expression and then inhibit the proliferation and angiogenesis of SCLC cells.[80] Moreover, cytochalasin H was found to reduce HIF-1α protein accumulation and downregulate VEGF through the PI3K/AKT/P70S6K and ERK1/2 pathways to suppress angiogenesis in NSCLC cells.[81] Similarly, Huaier downregulated HIF-1α and inhibited glycolysis in lung cancer both *in vivo* and *in vitro*, including glucose transport and lactic acid production, by inactivating the PI3K/AKT pathway.[82]

Hypoxia and reprogramming of glucose metabolism

Hypoxia is strongly associated with many metabolic adaptations in cancer that promote tumor cell growth and angiogenesis, an example of which is the adaptation of glucose metabolism. Glucose metabolism is also closely associated with glutamine and fatty acid metabolism. Hypoxia affects three main branches of glucose metabolism in tumor cells: the PPP, glycolysis, and OXPHOS [Figure 2]. First, HIF-1α is a positive transcriptional regulator of rate-limiting enzymes for the PPP, including glucose-6-phosphate dehydrogenase (G6PD). Glucose-6-phosphate (G6P), the substrate of G6PD, is utilized in the PPP as well as glycolysis to synthesize many key nucleotides (including ribonucleotides and deoxyribonucleotides) and amino acid precursors in cancer cell proliferation and growth. A recent study revealed that HIF-1α could regulate glucose metabolism and sensitivity to imatinib through the PPP in gastrointestinal stromal tumors.[83] Upon exposure to low-dose radiation, normal human cells were shown to exhibit HIF-1α-mediated metabolic alterations with reduced mitochondrial gene expression and enhanced expression of genes encoding glucose transporters and glycolysis and PPP enzymes.[84] Conversely, glucose metabolism through the PPP, rather than glycolysis, contributed to the stabilization of the HIF-1α protein under hypoxia.[85]

Second, 14 kinds of glucose transporters play important roles in glucose uptake, the first step of aerobic glycolysis. The most representative example is *GLUT-1*, an important transcriptional target of HIF-1α. Genetic alterations and hypoxia were found to increase *GLUT-1* expression in a HIF-1α-dependent manner, leading to increased glucose uptake and contributing to glycolysis and angiogenesis in SCLC cells.[86] Besides *GLUTs*, other important rate-limiting enzymes of glycolysis, such as pyruvate kinase M2 (PKM2), hexokinases (HKs), and LDHA, are positively regulated by HIF-1α. Hypoxia was shown to induce cisplatin resistance in NSCLC cells via exosomal PKM2, which transmitted the cisplatin resistance to sensitive tumor cells both *in vitro* and *in vivo* by promoting glycolysis, more antioxidant metabolite generation, and lethal-ROS (induced by cisplatin) neutralization.[87] Moreover, hypoxia increased *HKII* transcription in A549 NSCLC cells in a HIF-1-dependent manner.[88] In aerobic glycolysis, pyruvate generated in the last step is converted to lactate instead of acetyl coenzyme A in a HIF-1α-dependent manner under the action of LDHA, causing cancer acidosis in hypoxic regions. Subsequently, under the action of monocarboxylate transporter 4 (MCT4), which is also regulated by HIF-1α, lactate is removed from the cytoplasm to maintain the acid-base equilibrium of the tumor cells [Figure 2]. The outcome was a relatively alkaline intracellular environment favored by tumor cells and an acidic extracellular environment, which promoted extracellular matrix breakdown and increased the potential for metastasis[89] which is characteristic of SCLC.

Third, transient HIF-1α activation was shown to increase the levels of LDHA and the phosphorylated E1α subunit of pyruvate dehydrogenase (p-PDH-E1α) in lung cancer. This indicates that the switch in glucose metabolism from OXPHOS to glycolysis and lactic acid accumulation, and the HIF-1 inhibitor YC-1, suppressed the switch in glucose metabolism, elevated intratumoral ROS levels, and finally inhibited the metastasis of lung cancer.[90]

The PI3K/AKT/mTOR pathway and glucose metabolism

The PI3K/AKT/mTOR pathway can regulate glucose metabolism through HIF-1α and MYC, as discussed earlier. Other mechanisms of the PI3K/AKT/mTOR pathway in terms of regulating cancer glucose metabolism have also been identified. Cheng et al. reported that PI3K/AKT pathway activation inhibits ubiquitylation and degradation of G6PD, the key regulator of the PPP, by suppressing the E3 ligase TRIM21 and upregulating the PPP.[91] These authors also found that metabolites of the PPP enhance AKT activation and further promote the rewiring of glucose metabolism by downregulating the AKT inhibitor PHLDA3.[91] A recent study revealed that mTOR inhibition could reduce G6PD expression and NADPH levels and increase ROS levels, inducing ROS-dependent death in T-cell acute lymphoblastic leukemia.[92] Furthermore, a combination of baicalein, wogonin, and oroxylin-A was reported to suppress EMT progress through PI3K/AKT-TWIST1-glycolysis signaling in NSCLC cells.[93]

Targeting the PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism to improve radiotherapy efficacy

PI3K/AKT/mTOR pathway inhibition

Many small molecules have been developed as inhibitors of the PI3K/AKT/mTOR pathway. These small molecules can be classified into two major types, namely, single inhibitors that only inhibit PI3K, AKT, or mTOR signaling proteins, and dual inhibitors that block PI3K and mTOR signaling. Blocking the PI3K/AKT/mTOR pathway could enhance the sensitivity of cancer cells to radiation therapy. Clinical trials of combined PI3K/AKT/mTOR inhibitors and radiotherapy in solid tumors are summarized in Table 1.

The single PI3K inhibitor LY294002 enhances the cytotoxicity of low concentrations of etoposide by blocking AKT signaling in SCLC cells.[94] Similarly, the dual PI3K/mTOR inhibitor GSK2126458 can synergistically inhibit SCLC proliferation when combined with cisplatin and etoposide.[40] Furthermore, the dual PI3K and histone deacetylase inhibitor FK228 significantly potentiates the inhibitory effect of ionizing radiation on human radioresistant SCLC cells, mainly by inducing chromatin decondensation and impairing DNA repair competency.[95]

Hypoxia inhibition

Hypoxia target therapy focuses on applying bioreductive prodrugs and inhibiting molecular targets usually highly expressed in tumor cells. Oxygen itself is regarded as a radiosensitizer, and tumor-bearing mice are more susceptible to ionizing radiation when kept under oxygen pressure three times the normal atmospheric pressure compared with those under normal atmospheric pressure.[96] Bioreductive prodrugs selectively target and kill hypoxic cells. These prodrugs are metabolized under the strongly reductive conditions of hypoxic regions and then release the active drugs cytotoxic to the hypoxic cells. Therefore, the potential of these prodrugs to increase radiotherapy and chemotherapy efficiency makes them highly attractive in cancer therapy. Tirapazamine is one of the best characterized clinical bioreductive prodrugs, and several preclinical

Table 1
Summary of clinical trials of combined PI3K/AKT/mTOR inhibitors and radiotherapy in solid tumors.

Name of inhibitors	Targets	Year	Tumor types	Number of participants	ClinicalTrials.gov identifier or EU Clinical Trials Register	Phase	Radiotherapy dose (fraction no. X radiation)	Clinical observations
Voxtalisib	PI3K/mTOR	2015	Stage III-IV NSCLC	26	EudraCT No.2007-001698-27	I	28–66 Gy in 14–33 fractions	Pulmonary toxicity should be carefully monitored.
Voxtalisib	PI3K/mTOR	2015	High-grade GBM	54	NCT00704080	I	1.8–2 Gy/fraction up to 60 Gy, 5 days/week	A favorable safety profile and a moderate level of PI3K/mTOR pathway inhibition were observed.
Buparlisib	PI3K	2020	Newly diagnosed GBM	22	NCT01473901	I	30 × 2 Gy	A challenging safety profile of buparlisib in combination with radiotherapy and temozolomide was observed.
Alpelisib	PI3K	2020	Locoregionally advanced HNSCC	9	NCT02537223	I	35 × 2 Gy	Alpelisib at 200 mg had a manageable safety profile in combination with cisplatin-based chemoradiation.
Alpelisib	PI3K	2022	Stage III-IVB HNSCC	11	NCT02282371	I	33 × 2.12 Gy or 35 × 2 Gy	The recommended dose of alpelisib is 250 mg/d in combination with cetuximab and intensity-modulated radiation therapy.
Nelfinavir	PI3K/AKT	2016	Advanced rectal cancer	10	EudraCT No.2010-020621-40	NA	5 × 5 Gy, 7 days	Nelfinavir combined with radiotherapy is well tolerated and is associated with increased blood flow to rectal tumors.
Temsirolimus	mTOR	2014	NSCLC	10	NA	I	14 × 2.5 Gy, 5 days/week	The combination of temsirolimus 15 mg weekly and thoracic radiation is well tolerated.
Temsirolimus	mTOR	2010	Newly diagnosed GBM	12	NA	I	30 × 2 Gy	The increased infection rate with temsirolimus combined with chemo-radiotherapy was observed.
Rapamycin	mTOR	2007	Stage III NSCLC	7	NA	I	30 × 2 Gy	Combination therapy with rapamycin, radiation, and cisplatin was well tolerated.
Rapamycin	mTOR	2015	Primary resectable rectal cancer	13 (Phase I), 31 (Phase II)	NCT00409994	I/II	Short-course hypofractionated radiotherapy (5 × 5 Gy)	Obvious decrease in metabolic activity, but no significant pCR was found.
Everolimus	mTOR	2017	Locally advanced rectal cancer	12	EudraCT No.2010-022087-13	Ib	(28 × 1.8 Gy), 5 days/week	The manageable safety profile of everolimus combined with standard chemoradiation.
Everolimus	mTOR	2013	High-risk locally advanced prostate cancer	14	NCT00943956	I	37 × 2 Gy	Concomitant hormone-radiotherapy and everolimus were well-tolerated, and the recommended MTD of everolimus is 5 mg/day.
Everolimus	mTOR	2017	Prostate cancer with biochemical recurrence	18	NA	I	37 × 1.8 Gy	Everolimus at a dose of ≤10 mg/d is safe and tolerable in combination with fractionated post-prostatectomy radiotherapy.
Everolimus	mTOR	2016	Locally advanced cervix cancer	13	NCT01217177	I	25 × 1.8 Gy for radiotherapy and 4 × 6 Gy for brachytherapy	The MTD of everolimus in combination with cisplatin and radiotherapy was 5 mg/d.
Everolimus	mTOR	2011	Newly diagnosed GBM	18	NA	I	30 × 2 Gy	Everolimus combined with radiation and temozolomide was reasonably well tolerated.
Everolimus	mTOR	2015	Newly diagnosed GBM	100	NA	II	30 × 2 Gy	Combining everolimus with conventional chemoradiation had moderate toxicity.
Everolimus	mTOR	2018	Newly diagnosed GBM	171	NCT01062399	II	30 × 2 Gy	Combining everolimus with conventional chemoradiation increased treatment-related toxicities and did not improve PFS.

AKT: Protein kinase B; GBM: Glioblastoma; HNSCC: Head and neck squamous cell carcinoma; MTD: Maximum tolerated dose; mTOR: Mammalian target of rapamycin; NSCLC: Non-small cell lung cancer; pCR: Pathologic complete response; PI3K: Pphosphoinositide 3-kinase.

Table 2
Summary of drugs targeted against HIF-1 reaching clinical evaluation.

Name of drug	Mechanism of action	Tumor types	Number of participants	ClinicalTrials.gov identifier	Phase
EZN-2968	Antisense oligonucleotide inhibitor of HIF-1α	Advanced solid tumors with liver metastases	9	NCT01120288	I
RO7070179	HIF-1α mRNA antagonist	Hepatocellular carcinoma	9	NCT02564614	I
PX-478	Decrease HIF-1 accumulation by promoting ubiquitination and decreasing transcription and translation	Advanced solid tumors and lymphoma	45	NCT00522652	I
AFP464	Interfere HIF-1 mRNA	Advanced solid tumors	60	NCT00369200	I
Topotecan	Suppress HIF-1 translation via targeting topoisomerase I	Refractory advanced solid neoplasms expressing HIF-1 alpha	16	NCT00117013	I
Alvespimycin	Inhibit Hsp90, inducing HIF-1 degradation	Solid tumors and lymphomas	40	NCT00088868	I
STA-9090	Inhibit Hsp90, inducing HIF-1 degradation	Relapsed or refractory small cell lung cancer	25	NCT01173523	II
MBM-02	Inhibit both HIF-1α and HIF-2α	Prostate cancer in biochemical recurrence	55	NCT04876755	II
CRLX101	Inhibit the HIF→(CAIX) →VEGF→VEGFR2 pathway	Recurrent platinum-resistant ovarian, tubal, and peritoneal cancer	63	NCT01652079	II
EZN-2208	Suppress HIF-1 translation via targeting topoisomerase I	Metastatic breast cancer	160	NCT01036113	II
Digoxin	Suppress HIF-1 translation	Newly diagnosed operable breast cancer	6	NCT01763931	II

α: Alpha; HIF-1: Hypoxia-inducible factor.

studies have evaluated its synergistic efficacy with radiation treatment in lung cancer cell lines and mouse models.[97] Tirapazamine and radiation have been combined to treat refectory solid tumors in several clinical trials. For example, S0004, a phase I clinical trial, evaluated the addition of tirapazamine to cisplatin/etoposide and once-daily thoracic radiotherapy among patients with LS-SCLC; the ORR was 80%, and the median OS was 22 months.[98] Subsequently, the phase II trial SWOG 0222 was initiated but had to be terminated early because a parallel trial reported excessive toxicity.[99] The results of SWOG 0222 were similar to those of S0004 in that the ORR was 63%, median progression-free survival was 11 months, and median OS was 21 months, but 46% of patients presented with grade 4 adverse events, mainly from hematologic toxicity. Although tirapazamine was not investigated further, targeting hypoxia for SCLC treatment remains an attractive prospect.

Many drugs have been found to suppress the expression of HIF-1α and its target genes and have entered clinical trials, as summarized in Table 2. A phase Ib/II clinical trial reported acceptable toxicity levels among patients with relapsed or refractory SCLC treated with ganetespib plus doxorubicin, highlighting the potential of ganetespib for SCLC treatment.[100] Admittedly, there are some limitations to targeting HIF-1 in cancer treatment. First, owing to the multiple isoforms of HIF-1, a potential functional redundancy can limit the efficacy of targeting HIF-1. Second, HIF-1 is also expressed in non-hypoxic regions and normal tissues, which could lead to possible off-target effects. Third, 10%–20% of patients with SCLC present with brain metastasis at the time of initial diagnosis, and 50%–80% of patients finally develop brain metastasis during the therapeutic process.[101] Therefore, the blood-brain barrier permeability of drugs targeting hypoxia should be comprehensively evaluated in preclinical and clinical studies.

Glucose metabolism inhibition

Multiple drugs targeting pivotal enzymes or transporters in glucose metabolism have been identified, some of which have entered preclinical and/or clinical trials.[63,64] Clinical trials of these drugs in combination with radiotherapy are summarized in Table 3. WZB117 is a selective inhibitor of GLUT-1 shown to inhibit glucose metabolism in breast cancer; it also re-sensitizes radioresistant breast cancer cells to radiation.[102] Lonidamine is the first orally administered small-molecule inhibitor of mitochondria-bounded hexokinase to suppress glycolysis. 2DG is structurally similar to glucose, and mechanically, this molecule competitively inhibits HK2, which regulates the first rate-limiting step of glycolysis. In addition, 3-BrPA was found to inhibit glycolysis, disturb redox homeostasis, and decrease nucleotide synthesis in triple-negative breast cancer, finally enhancing the inhibitory effect of ionizing radiation.[103]

Table 3
Clinical trials of targeting enzymes or transporters of glucose metabolism in the combination of radiotherapy in solid tumors.

Name of inhibitors	Targets	Year	Tumor types	Number of participants	Phase	Radiotherapy schedule	Clinical observations
Lonidamine	Hexokinase	1994	Clinically localized but nonresectable NSCLC	310	III	1.8 Gy/fraction up to 55–60 Gy, 5 days/week	No significant advantages in the lonidamine-treated population in OS, PFS, and the median duration of local control were observed.
Lonidamine	Hexokinase	1994	Stages II-IV HNSCC	97	III	1.5 Gy/fraction up to 60–65 Gy	The addition of lonidamine to hypofractionated radiotherapy was correlated with longer DFS.
Lonidamine	Hexokinase	1989	Brain metastases	58	II	3000 cGy of WBRT	No serious organ toxicity or myelosuppression was observed.
2-deoxy-D-glucose	Hexokinase	1996	Supratentorial GBM (grade III/IV)	20	I/II	4 × 5 Gy/fraction/week, WBRT	The feasibility of administering the treatment (2-deoxy-D-glucose + 5 Gy) was well tolerated.
2-deoxy-D-glucose	Hexokinase	2006	Grade IV GBM	70	II	7 × 5 Gy/fraction/week to residual tumor +3 cm margin	Restlessness in a few patients. No life-threatening changes in vital parameters.
Dichloroacetate	Pyruvate dehydrogenase kinase	2022	Unresected, locally advanced HNSCC	45	II	35 × 2 Gy	Adding dichloroacetate to cisplatin-based chemoradiotherapy appeared safe with no detrimental effect on survival and expected metabolite changes.

DFS: Disease-free survival; GBM: Glioblastoma; HNSCC: Head and neck squamous cell carcinoma; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; WBRT: Whole-brain radiotherapy.

Another important glycolytic enzyme, pyruvate dehydrogenase kinase (PDK), can similarly be targeted using specific small-molecule inhibitors. PDK participates in regulating the rate and amount of pyruvate entering the tricarboxylic acid cycle by inhibiting dehydrogenase activity. Some studies reported that PDK suppression alters glucose metabolism and elevates oxygen consumption in cancer cells, finally increasing ROS production and susceptibility to ionizing radiation.[104–106] Dichloroacetate (DCA) is a kind of small-molecule inhibitor that can reverse the glycolytic phenotype and suppress cell proliferation and angiogenesis.[106] In combination with ionizing radiation or anticancer platinum compounds, DCA has shown a synergistically inhibitory effect against several types of cancer cell lines, including those for SCLC and NSCLC.[107,108] Similarly, a recent study on NSCLC revealed that DCA combined with EGFR tyrosine kinase inhibitors and/or radiotherapy significantly increased the cytotoxic effects by redirecting glucose metabolism toward OXPHOS and decreasing lactate generation.[109]

LDHA is a specific inhibitor of FX-11 that can enhance the radiosensitivity of prostate cancer cells with acquired radioresistance by decreasing EMT, hypoxia, and autophagy and increasing DNA double-strand break events and apoptosis.[110] Furthermore, AZD3965, in combination with fractioned radiation, was more efficacious at inhibiting monocarboxylate transporter 1 (MCT1) than using either modality alone in SCLC xenografts.[111] The carbonic anhydrase inhibitor indisulam can also apparently suppress tumor cell growth and sensitize GBM cells to radiotherapy and chemotherapy.[112]

Conclusion

SCLC is a fast-growing, highly aggressive cancer with a poor prognosis and limited effective therapy options. The rapid emergence of radiotherapy resistance in SCLC is a key contributor to treatment failure and poor survival. PI3K/AKT/mTOR pathway activation and hypoxia are known mechanisms underlying radioresistance. The PI3K/AKT/mTOR pathway can increase HIF-1α expression at the transcription level, and both the PI3K/AKT/mTOR pathway and HIF-1α play key roles in regulating the expression of key enzymes and/or transporters in glucose metabolism, including glycolysis, OXPHOS, and the PPP. Herein, we summarized promising avenues of research and provided insights into potential treatments to promote cancer cell death and improve the clinical prognosis of patients with this devastating disease. Admittedly, the relationship among the PI3K/AKT/mTOR pathway, hypoxia, and glucose metabolism is complex, and further studies should concentrate on how these signaling pathways interact to influence SCLC radioresistance.

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Author contributions

Huan Deng takes responsibility for the integrity of the data and the accuracy of the analysis. Drafting of the manuscript: Huan Deng and Ying Jin. Supervision: Ying Jin and Ming Chen. Concept and design: All authors. Acquisition, analysis, and interpretation of data: All authors. Critical revision of the manuscript for important intellectual content: All authors. All authors read and approved the final manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None.

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