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GBE1 INHIBITION: ALTERNATIVE THERAPY FOR LUNG CANCER BY ALTERING GLUCOSE METABOLISM

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Abstract

Lung cancer represents a neoplastic malignancy within pulmonary tissue and is associated with the highest mortality rate attributed to cancer globally. Non-Small Cell Lung Cancer (NSCLC) constitutes the predominant category of lung cancer, accounting for approximately 80-85% of all diagnosed cases, with adenocarcinoma subtyping comprising nearly 40% of NSCLC instances. Despite advancements in surgical techniques and diverse therapeutic modalities, the five-year survival rate remains below 20%, necessitating ongoing research endeavors aimed at the enhancement of lung cancer treatment paradigms. This review investigates the intricate interplay between Glycogen Branching Enzyme 1 (GBE1) and metabolic reprogramming, as well as its interaction with hypoxic environments and subsequent effects on the phenotypic characteristics of lung cancer cells. Hypoxic conditions frequently manifest in solid tumors, including lung cancer, eliciting adaptive responses such as the activation of Hypoxia-Inducible Factor-1 alpha (HIF1α), which subsequently initiates angiogenesis, induces metabolic alterations, and contributes to therapeutic resistance. Glycogen Branching Enzyme 1 (GBE1) serves as a critical enzyme involved in the synthesis of glycogen branching structures. In the context of lung adenocarcinoma (LUAD), GBE1 operates within the downstream signaling cascade of the Hypoxia-Inducible Factor-1 (HIF1) pathway. This review aspires to furnish novel insights into the pathogenesis of lung cancer and to assess the strategic targeting of the HIF1α/GBE1/NF-κB/FBP1 axis as a promising therapeutic approach for LUAD.

Keywords: GBE1, Hypoxia, Glycogen, NSCLC, Metabolic Reprogramming

Introduction

Lung cancer constitutes a significant global health challenge and represents the predominant etiology of cancer-associated mortality on a worldwide scale. According to statistics derived from GLOBOCAN (Global Cancer Observatory) in 2020, the incidence of lung cancer is positioned as the second most prevalent, contributing approximately 11.4% to the overall cancer case count (Oser et al., 2015; Sung et al., 2021). Despite notable advancements in the realms of early detection and the formulation of effective targeted therapies and immunotherapies, the five-year survival rate for individuals diagnosed with advanced lung cancer remains below 20% (Sánchez-Ortega et al., 2021); (Hynds et al., 2021). This situation severely compromises the quality of life for patients afflicted with lung cancer, adversely impacting their social and familial interactions, in addition to incurring substantial and protracted treatment expenditures. Research related to lung cancer treatment or therapy needs to continue.

Histologically, lung cancer is categorized into two primary classifications: Small-Cell Lung Cancer (SCLC; approximately 15% of cases) and Non-Small-Cell Lung Cancer (NSCLC; approximately 85% of cases). NSCLC is further subdivided into three distinct sub-types predicated primarily on the morphological characteristics of the

transformed cells: Adenocarcinoma (LUAD), Squamous-Cell Carcinoma (LUSC), and Large-Cell Carcinoma (LCC) (Cardona et al., 2020; Oser et al., 2015). In the case of Small-Cell Lung Cancer, the neoplastic growth originates from neuroendocrine lineage cells following the inactivation of RB and TP53, whereas in Non-Small-Cell Lung Cancer types, the tumors arise from lung epithelial cells subsequent to various genetic alterations. LUAD evolves from alveolar type II (AT2) epithelial cells or cells situated at bronchioalveolar duct junctions, while LUSC is derived from basal epithelial cells located within the airways (Zhao Chen et al., 2014; Sánchez-Ortega et al., 2021). LUSC differentiates into a stratified squamous epithelium, a feature absent in non-keratinizing epithelial tissues. The third sub-type of NSCLC, LCC, also emanates from lung epithelial cells and signifies a heterogeneous assemblage of malignant neoplasms that do not exhibit the cytological or architectural traits characteristic of small cell or glandular carcinoma (LUAD) or squamous (LUSC) sub-types. All variants of lung cancer exhibit a dismal prognosis, particularly SCLC and LUSC, which are typically prevalent among tobacco users (Cardona et al., 2020); (Hynds et al., 2021). Conversely, LCC tends to have a relatively more favorable prognosis, contingent upon the specific sub-type. LUAD predominantly manifests in individuals with no prior significant exposure to tobacco and is recognized as the most common form (Cardona et al., 2020; Sánchez-Ortega et al., 2021).

The pulmonary system exhibits a distinctive environment in which neoplasms develop in conjunction with the tumor microenvironment (TME), as demonstrated by areas of abnormal angiogenesis (Mittal et al., 2016); (C. Liu et al., 2021), acidosis (Mittal et al., 2016), stromal cell formation (C. Liu et al., 2021), and hypoxia (Y. Li et al., 2021); (Ziółkowska-Suchanek, 2021). Solid tumors emerge in the absence of a pre-existing vascular network and can only sustain themselves by enlisting new blood vessels, which are perpetually insufficient and dysfunctional. The rapid proliferation of neoplastic cells typically culminates in oxygen depletion and resultant hypoxia within most tumor microenvironments. Neoplastic cells residing in these hypoxic niches commence adaptation to low oxygen tension by upregulating Hypoxia Inducible Factors (HIFs), specifically HIF1α and HIF2α, which facilitate the transcriptional activation of genes implicated in angiogenesis (Mittal et al., 2016), cellular survival (Masoud & Li, 2015), and chemoresistance (L. Ma & Zong, 2020); (Kim & Lee, 2017). Empirical evidence suggests that hypoxia can exacerbate tumor aggressiveness and adversely affect clinical prognosis. Under hypoxic conditions, cancer cells adapt to sustain tumor proliferation through metabolic reprogramming, characterized by the Warburg effect, glycogen accumulation, and a metabolic switch from glucose to glutamine as the principal substrate for lipogenesis (C. Liu et al., 2021); (Zhou Chen et al., 2023); (Kim & Lee, 2017). In 1924, Otto Warburg elucidated the hypothesis that tumors extensively utilize glucose for their sustenance. The majority of glucose metabolized by tumors is converted into lactate rather than being oxidized via pathways dependent on aerobic respiration. This understanding may provide insights into the tumor microenvironment that are essential for the identification of biomarkers and the development of novel targeted therapies for lung cancer (C. Liu et al., 2021); (L. Ma & Zong, 2020).

Prior investigations have established that, under hypoxic conditions, lung cancer cells enhance the expression of HIF1α, which subsequently upregulates the transcription of Glycogen Branching Enzyme 1 (GBE1) (L. Li et al., 2019); (L. Li et al., 2020). GBE1 is pivotal in glycogen biosynthesis, facilitating the formation of α-1,6-glucosidic branches from α-1,4-linked glucose polymers to augment the solubility of the glycogen molecule.

Genetic mutations affecting the GBE1 gene are associated with the heterogeneous early-onset Glycogen Storage Disorder type IV (GSD-IV) and the late-onset Adult Polyglucosan Body Disease (APBD) (Z. Ma et al., 2022); (Froese et al., 2015). GBE1 is positioned downstream of the transcription factor HIF1α. In hypoxic lung cancer cells, HIF1α becomes activated, translocating from the cytoplasm to the nucleus, where it functions as a transcription factor and induces the transcription of GBE1. The overexpression of GBE1 elevates glucose concentrations, potentially facilitating a transition to the Warburg effect (L. Li et al., 2019); (L. Li et al., 2020). Furthermore, GBE1 expression has the capacity to downregulate Fructose-1,6-Bisphosphatase 1 (FBP1) expression through methylation of the promoter region via NFkB signaling within the tumor microenvironment under hypoxic conditions. A reduction in FBP1 expression will result in increased levels of HIF1α, thereby instigating a metabolic shift from oxidative phosphorylation to anaerobic glycolysis and enhancing glucose uptake (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022). The significance of GBE1 in the proliferation of lung cancer cells is further corroborated by evidence indicating that GBE1 gene expression is markedly elevated in Lung Adenocarcinoma (LUAD) cells compared to adjacent normal tissues (Zhen Chen et al., 2023; Froese et al., 2015; L. Li et al., 2017; Z. Li et al., 2023; Liang et al., 2022; Z. Ma et al., 2022; Pavlova et al., 2022; Ziółkowska-Suchanek, 2021).

The conventional therapeutic regimen for lung adenocarcinoma encompasses traditional chemotherapy, radiotherapy, targeted therapy, immunotherapy, and lobectomy. This treatment modality is associated with adverse effects, including unintended cytotoxicity to non-targeted cells (Chalela et al., 2017; Girard et al., 2024; Herbst et al., 2018; Saito et al., 2018; Wang, 2022; Zappa & Mousa, 2016). Two missense mutations frequently observed in GSD-IV are L224P and Y329S. The L224P mutation leads to a complete abrogation of GBE1 activity, while the Y329S mutation results in approximately 50% reduction of GBE1 activity (Bao et al., 1996). Both GBE1 interventions may be utilized as molecular agents to inhibit the GBE1 gene via gene therapy approaches. Numerous genes have been investigated as candidates for gene therapy; however, the GBE1 gene exhibits the most promising potential as a target (Melendez et al., 1999; Thon et al., 1993). Inhibition of GBE1 is aimed at diminishing functional enzyme levels, gene expression, and activation within the context of lung carcinoma. A reduction in GBE1 gene expression is anticipated to induce apoptosis in neoplastic cells through the activation of lymphocytes (L. Li et al., 2019). GBE1 serves as a crucial factor in tumorigenesis, and it is posited that GBE1 inhibition could represent a viable therapeutic target for lung cancer through gene therapy strategies that exploit the HIF α signaling pathway in the foreseeable future (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022); (L. Li et al., 2017).

Result and Discussion

Hypoxia Mechanisms in Tumor Microenvironment

Hypoxia represents the most prevalent microenvironmental characteristic associated with lung malignancies. This hypoxic condition is linked to all the fundamental attributes of cancer as delineated by Hanahan and Weinberg (Hanahan, 2022). Hypoxia is defined by a deficiency of molecular oxygen (O2), and tissues affected by hypoxia exhibit insufficient functionality. The presence of a hypoxic microenvironment has been documented across various tissue types, wherein both normal and neoplastic cells adapt to such environments through the modulation of hypoxia-inducible factor (HIF)

transcription factors. HIF comprises dimeric proteins that are formed by an O2-sensitive α subunit (namely HIF-1α, HIF-2α, and HIF-3α) and a β-subunit (HIF-1β/aryl hydrocarbon receptor nuclear translocator) (Noman et al., 2015). HIF-1α and HIF-2α are subjected to regulation via O2-dependent degradation mediated by the Von Hippel-Lindau (VHL) tumor suppressor, as well as through oncogenic gain of function, which enhances PI3K/AKT/mTOR signaling pathways; these factors collectively orchestrate metabolic modifications that facilitate cancer progression and confer resistance to therapeutic interventions (C. Liu et al., 2021; Masoud & Li, 2015; Semenza, 2013). HIF-1α is expressed ubiquitously, whereas HIF-2α is selectively expressed in specific cell types, including hepatocytes and endothelial cells. Numerous cancers exhibit regions of intratumoral hypoxia, and primary tumors characterized by diminished oxygenation (PO2 < 10 mmHg) correlate with an elevated risk of mortality (Zhou Chen et al., 2023; Kim & Lee, 2017; Y. Li et al., 2021; C. Liu et al., 2021; L. Ma & Zong, 2020; Masoud & Li, 2015). Lung cancers are typified by a pronounced glycolytic rate, as the hypoxic conditions compel tumor cells to transition from oxidative phosphorylation to glycolysis, consequently leading to the generation of metabolic acids (Pugachev et al., 2005; Shen et al., 2017; G. Zhang et al., 2015).

Glycolysis constitutes a pivotal metabolic pathway for glucose catabolism that can transpire under both aerobic and anaerobic conditions. This metabolic pathway serves two principal functions: the degradation of glucose to yield adenosine triphosphate (ATP) through catabolic processes and the provision of essential precursors for biosynthetic activities (Wanandi et al., 2018). Glycolysis comprises a series of enzymatically catalyzed reactions that involve enzymes such as hexokinase, phosphofructokinase, and pyruvate kinase. Each of these enzymes facilitates distinct biochemical reactions within the glycolytic pathway, thereby acting as regulatory points for the overall glycolytic rate (Lee & Yoon, 2015).

In neoplastic cells, often referred to as glycolytic cells, glucose is metabolized into lactate even in the presence of sufficient oxygen within the microenvironment. This phenomenon is termed the Warburg Effect (Hsu & Sabatini, 2008). Lactate dehydrogenases (LDHs) are critical metabolic enzymes that play a significant role in the pivotal step of lactate interconversion. Numerous studies have suggested that the expression and activity of LDH may serve as a biomarker to assess the metabolic state of cancer cells (Draoui & Feron, 2011; Jurisic et al., 2015). The surplus lactate generated by glycolytic tumor cells is extricated from the tumor microenvironment through uptake by cancer-associated fibroblasts (CAFs), which function as oxidative cells. The lactate absorbed by CAFs is utilized as an energy source by integrating it into oxidative phosphorylation occurring within the mitochondria. Contrarily, in alignment with the Warburg effect, glycolytic cells within the microenvironment have the capacity to export lactate to adjacent tumor cells—termed oxidative cells—which subsequently utilize lactate for oxidative phosphorylation, a process referred to as the reverse Warburg effect (Lee & Yoon, 2015). Monocarboxylate Transporters (MCTs) work in conjunction with LDHs to facilitate lactate transport, which ultimately converts pyruvate into lactate during the final stage of anaerobic glycolysis (Draoui & Feron, 2011); (Rattigan et al., 2012).

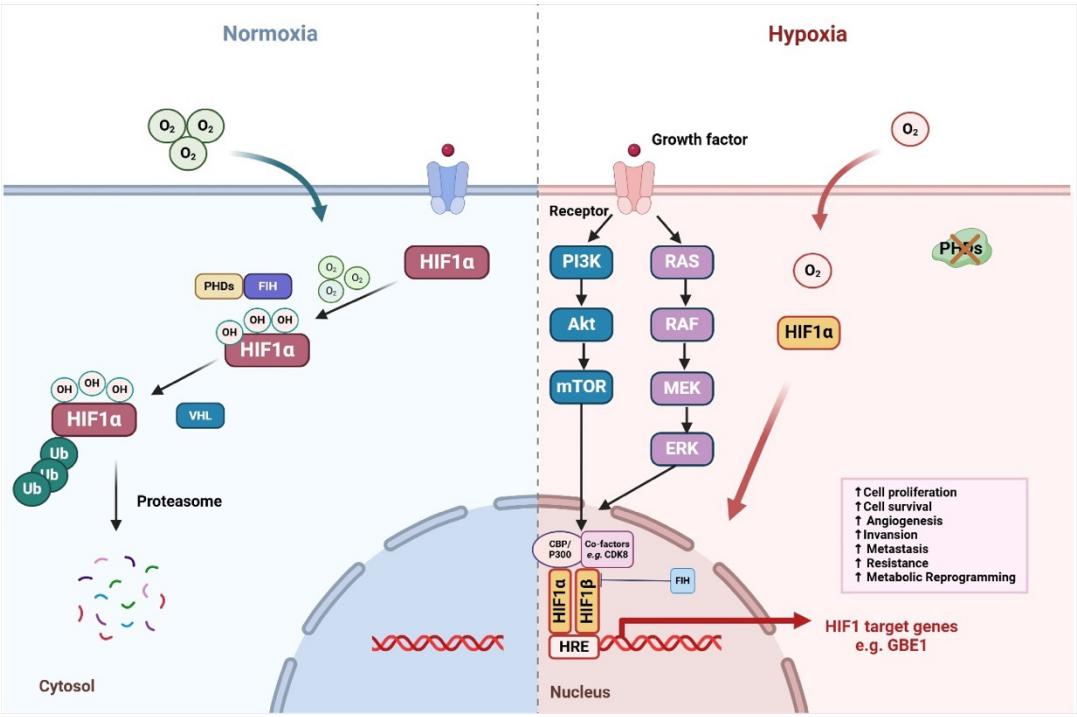


Figure 1. Lung Cancer Pathogenesis by GBE1 through HIF1α Signaling.

In normoxic conditions, HIF-1α undergoes hydroxylation mediated by prolyl-4-hydroxylase (PHD) and factor inhibiting HIF-1 (FIH), subsequently associating with von Hippel-Lindau (VHL), which facilitates its proteasomal degradation. Conversely, under hypoxic conditions, HIF-1α is spared from ubiquitylation and degradation, resulting in its accumulation and subsequent translocation to the nucleus, culminating in the formation of a heterodimeric complex composed of HIF-1α and HIF-1β. These complexes then engage with the hypoxia response element (HRE) in conjunction with p300/CBP and various co-factors, thereby initiating the transcriptional activation of numerous genes, including Glycogen Branching Enzyme 1 (GBE1). Figure created with https://BioRender.com (accessed on 11 December 2024).

Here, we mainly focus on the influence of hypoxia on metabolic reprogramming in lung cancer and its effects on tumor progression. Previous research on lung cancer cells shows that HIF1α in upregulating the transcription of GBE1, modulates tumor cells to adapt to the Warburg effect (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022). HIF-1α also mediates metabolic reprogramming in CAFs by upregulating the expression of MCT4 and subsequently downregulating caveolin-1 to supply energy to the growing tumor cells (Shen et al., 2017). Tumor cells switch their metabolic state between glycolysis and oxidative phosphorylation through metabolic interplay with CAFs and exhibit the Warburg effect under hypoxia and the reverse Warburg effect under normoxia. This metabolic interplay is critical as it further promotes tumor growth and metastasis (Yan et al., 2015). Tumor cell-derived ROS decreases the expression of caveolin-1 in CAFs which further stabilises HIF-1α (Wanandi et al., 2018); (Yoshida, 2015). This metabolic symbiosis, however, does not occur equally in all tumor types and accounts for tumor heterogeneity in the same tumor and thus significantly affects therapeutic strategies and chemoresistance (Yoshida, 2015).

Function of GBE1 (Glycogen Branching Enzyme 1) In Glycogen Metabolism.

Glycogen branching enzyme 1 (GBE1) serves a pivotal function in glycogen biosynthesis by facilitating the formation of α-1,6-glucosidic branches from α-1,4-linked glucose chains, thereby augmenting the solubility of the glycogen polymer (Z. Ma et al., 2022); (Froese et al., 2015). Predominantly localized in hepatic and muscular tissues, GBE1 acts as a glycogen-branching enzyme and is integral to the incorporation of glucosyl units into the glycogen chain, which is crucial for both glycogen accumulation and the enhancement of its solubility (Froese et al., 2015); (Thon et al., 1993). GBE1 is situated downstream of the Hypoxia-Inducible Factor-1 (HIF1) signaling axis in lung adenocarcinoma (LUAD). The upregulation of GBE1 induced by hypoxia mediates metabolic reprogramming in LUAD cells. Hypoxic conditions prompt a metabolic transition from oxidative phosphorylation to glycolysis and stimulate glycogen synthesis (Zhen Chen et al., 2023; Kim & Lee, 2017; L. Li et al., 2019, 2020; Liang et al., 2022). Glucose serves a significant role in cancer metabolism via glycolytic and anabolic pathways, with cancer cells converting pyruvate into lactate. The pentose phosphate pathway (PPP) diverges from glycolysis, yielding ribose and NADPH (Stine et al., 2014).

Mutations in GBE1 have been documented to correlate with Adult Polyglucosan Body Disease (APBD) and Glycogen Storage Disease Type IV (GSD-IV) (Choi et al., 2018; W. Jin et al., 2024); (Bao et al., 1996). Nevertheless, an increasing corpus of literature has underscored its relevance in oncology. On the one hand, GBE1 is markedly expressed in Acute Myeloid Leukaemia (AML), where it sustains aberrant tumor cell proliferation by inhibiting AMPK activity (Bhanot et al., 2015). Furthermore, GBE1 expression is elevated in lung adenocarcinomas and correlates with inferior survival outcomes.[19] Conversely, GBE1 expression is diminished in ovarian cancer, with GBE1 downregulation being associated with adverse clinical prognoses (Lando et al., 2009). Additionally, GBE1 is upregulated in pancreatic cancer (PC), correlating with unfavorable patient prognostics, as it bolsters cell proliferation and stemness by stabilizing c-Myc through m6A modification, thereby indicating its oncogenic potential (W. Jin et al., 2024). Elevated levels of GBE1 are also linked to poor survival rates in melanoma patients undergoing treatment with checkpoint inhibitors such as anti-PD1 (Buart et al., 2017). Recently, GBE1 has been identified as an oncogene involved in the cellular growth (L. Li et al., 2020), migration (Liang et al., 2022), glycolysis (Zhen Chen et al., 2023), and anti-tumor immunity of lung adenocarcinoma (LUAD) (L. Li et al., 2019). These investigations illustrate that GBE1 assumes divergent roles across various tumor types and is intricately linked to metabolic tumors. Consequently, targeting tumor metabolism may provide a multifaceted approach to inhibit tumor progression.

GBE1 Expression In Lung Cancer Compared With Normal Tissue.

Previous research indicates that the mRNA expression levels of GBE1 and HIF1α were significantly elevated in LUAD cells (A549) compared to those in normal lung cells (16HBE). The expression of GBE1 protein was likewise significantly greater in LUAD tissues in comparison to normal lung tissues. Furthermore, the expression of FBP1 was considerably diminished in tumor tissues relative to normal lung tissues (L. Li et al., 2019, 2020). Under conditions of hypoxia, the proliferation and energy metabolism of normal cells are adversely affected, whereas cancer cells exhibit adaptive mechanisms to sustain tumor proliferation by transitioning from oxidative phosphorylation to oxygen-independent glycolysis. It has been demonstrated that glycogen is instrumental in fostering cell survival under hypoxic conditions in both normal and cancerous cells.

Additionally, research has proposed that the transfer of glucose through glycogen may serve to enhance the survival of tumor cells subjected to hypoxic environments (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022). (Figure 1).

Table 1. Comparison of GBE1 Expression in Various Cancer

Cancer Type	Sample	Phenotype	Reference
Cervical Cancer	Patient sample	GBE1 downregulation is correlated with poor clinical outcomes	(Lando et al., 2009)
Acute Myeloid Leukemia (AML)	Cell line KU812, patient sample, mouse sample	High levels of GBE1 enzymes are linked to worse survival in acute myeloid leukemia (AML)	(Bhanot et al., 2015)
Melanoma	Patient sample, Cell lines ME204AI/ER, ME260 LN/DG, T921 DUF/ALE, ME300PB, ME290Mh, NA8, M74RIOUP, T1 and G1, M4T and M4T2, RAYI2 and M1. PBMC sample.	The elevated levels of GBE1 are associated with poor survival rates in melanoma patients treated with checkpoint inhibitors like anti-PD1 (pembrolizumab) immunotherapy	(Buart et al., 2017)
Lung Adenocarcinoma	Patient sample, Cell line A549, PBMC, xenofraft model in nude mice.	GBE1 plays a key role in T cell movement into tumors, and its blockage can increase chemokine levels CXCL10 and CCL5 to recruiting $CD8^{+}$T cells to tumor sites and efficiency PD-L1 therapy.	(L. Li et al., 2019)
	Patient sample, Cell lines A549, 16-HBE, xenofraft nude mice model	High GBE1 correlates with poor survival in LUAD patients	(L. Li et al., 2020)
	Patient sample, LUAD tissues	GBE1 expression is higher in LUAD tissues than normal tissues, and higher GBE1 correlates with poorer prognosist in LUAD patients	(Liang et al., 2022)
Glioma	Cell lines U87, U251, HEK293T, HUVECs, LN229, BALB-c nude male mice aged 4-6 weeks (xenograft)	GBE1 is elevated in gliomas, linked to poor prognosis	(Zhen Chen et al., 2023)
Pancreatic Cancer	Cell lines BXPC3, SW1990	GBE1 overexpression enhanced cell growth and stemness-like properties of pancreatic cancer cells	(W. Jin et al., 2024)

Relationship Between GBE1, Glycogen Metabolism, and Hypoxia in the Tumor Microenvironment

Hypoxia refers to a physiological state characterized by a deficiency of oxygen in cellular or tissue environments. The presence of hypoxia within neoplastic cells is regarded as a commonplace phenomenon. It is well-established that hypoxia triggers the activation of the unfolded protein response (Bartoszewska et al., 2022; Mujcic et al., 2009), a mechanism that can potentiate tumor proliferation through the secretion of proinflammatory cytokines (Grootjans et al., 2016). Consequently, it is plausible that the accumulation of glycogen may further amplify this signaling cascade (Vernia et al., 2009). The signaling pathway of HIF1α is situated as a downstream effector within the PI3K/Akt/mTOR signaling axis. Primarily, the PI3K/Akt/mTOR pathway serves as a

pivotal regulator of cellular energy homeostasis and metabolic processes, subsequently enhancing glycolytic activity and fatty acid synthesis through the activation of HIF1α and sterol regulatory element-binding protein (SREBP), respectively (J. Li et al., 2020); (Mafi et al., 2023). Hypoxia elicits a cellular adaptive mechanism that results in the upregulation of transcription factors known as hypoxia-inducible factors (HIFs), which orchestrate widespread alterations in gene expression across both non-malignant and malignant cell types (Nisar et al., 2023).

In solid tumors such as lung carcinoma, cellular proliferation and angiogenesis occur extensively within the tissue, subsequently leading to a deficiency of oxygen. Consequently, signal transduction pathways are activated due to proliferation and angiogenesis, which subsequently induce the expression of HIF1α (Maruggi et al., 2019). The HIF1α protein resides in the cytosol. Under conditions of cellular hypoxia, HIF1α becomes activated and translocates to the nucleus, functioning as a transcription factor. The activation of HIF1α modulates the expression of genes implicated in cancer malignancy, including those involved in angiogenesis, invasion, metastasis, and metabolic reprogramming. A notable gene subject to transcriptional regulation by HIF1α is the GBE1 gene. HIF1α enhances the transcriptional activity associated with the GBE1 gene. The overexpression of GBE1 leads to elevated glucose concentrations, potentially augmenting the Warburg effect. Furthermore, the increased expression of GBE1 can inhibit the expression of Fructose-1,6-Bisphosphatase 1 (FBP1) through methylation in the promoter region, mediated by the transcription factor Nuclear Factor kappa B (NFκB) within the tumor microenvironment under hypoxic conditions. A reduction in FBP1 expression signifies an elevation in HIF1α expression, which may instigate a metabolic transition from oxidative phosphorylation to anaerobic glycolysis, thereby enhancing glucose uptake (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022); (Zhu et al., 2015). It has been demonstrated that GBE1 orchestrates the metabolic reprogramming of LUAD cells. The expression levels of gluconeogenesis pathway molecules, particularly fructose-1,6-bisphosphatase (FBP1), were significantly elevated in shGBE1 A549 cells in comparison to the control cells (L. Li et al., 2020). Conversely, the capacity for cell proliferation and colony formation was significantly diminished, while the rate of cell apoptosis was markedly increased (L. Li et al., 2019, 2020; Liang et al., 2022).

Glucose homeostasis is modulated reciprocally by the catabolic pathways of glycolysis/oxidative phosphorylation (OXPHOS) and the anabolic gluconeogenesis pathway. Dysregulated glucose metabolism facilitates tumorigenesis and progression across various cancer types (Petersen et al., 2017). As initially described in the 1920s, certain tumor cells preferentially utilize glycolysis over OXPHOS, even in the presence of sufficient oxygen, a phenomenon referred to as “aerobic glycolysis” or the “Warburg effect” (Warburg, 1956). Although prior research has predominantly focused on aberrant glycolysis, there has been limited investigation into the role of gluconeogenesis, the reciprocal metabolic counterpart to glycolysis, in the context of cancer. Fructose-1,6-bisphosphatase (FBP1), recognized as one of the rate-limiting enzymes in gluconeogenesis, catalyzes the hydrolysis of fructose-1,6-bisphosphate (F-1,6-P2) to fructose 6-phosphate (F-6-P) and inorganic phosphate (G.-M. Liu et al., 2018). In mammalian organisms, two isoenzymes of FBP exist: FBP1 and FBP2. While the expression of FBP2 is confined to muscular tissue, FBP1 is more broadly expressed throughout various tissues (Marín-Hernández et al., 2006). An autosomal recessive inherited disorder characterized by FBP1 deficiency manifests as hypoglycemia and lactic

acidosis, often resulting in sudden infant death syndrome. This observation suggests that the absence of FBP1 enhances glucose uptake and glycolysis, consequently leading to hypoglycemia and lactic acidosis in affected individuals (C.-H. Li et al., 2022; J. Zhang et al., 2016).

FBP1 operates as a tumor suppressor by facilitating glycogen biosynthesis and restraining glycolytic pathways in various cancer types (Lu et al., 2020). Nonetheless, the non-canonical roles of FBP1 are not contingent upon its enzymatic capabilities. For instance, the non-canonical variant of FBP1 serves as a co-suppressor for numerous transcription factors, inclusive of HIF-1α (B. Li et al., 2014); (Lu et al., 2020). In recent findings, FBP1 has been indicated to exert suppressive influences across multiple malignancies, encompassing renal cancer (B. Li et al., 2014), breast cancer (Dong et al., 2013; Shi et al., 2017), lung cancer (J. Zhang et al., 2016); (Semenza, 2013), pancreatic cancer (Zhu et al., 2015); (X. Jin et al., 2017), hepatocellular carcinoma (G.-M. Liu et al., 2018), colon cancer, and gastric cancer (X. Liu et al., 2010). To date, the predominant mechanism elucidating the suppression mediated by FBP1 has been identified as promoter DNA methylation (Zhu et al., 2015); (Mafi et al., 2023); (G.-M. Liu et al., 2018); (J. Zhang et al., 2016); (B. Li et al., 2014); (Dong et al., 2013); (X. Jin et al., 2017); (X. Liu et al., 2010); (Shi et al., 2017). In the context of lung cancer, the methylation observed in the promoter region of FBP1 is mediated by the transcription factor NFκB within the tumor microenvironment under hypoxic conditions. Nevertheless, the mechanisms that underlie the Warburg effect remain significantly ambiguous (L. Li et al., 2019, 2020; Liang et al., 2022). Prior investigations have indicated that the Rat Sarcoma (RAS)/NF-κB: Nuclear Factor-Kappa B (NF-κB) signaling pathway facilitates the DNA methylation of FBP1 in gastric cancer cells (X. Liu et al., 2010).

NF-κB constitutes a transcription factor that is integral to inflammatory responses and represents one of the most critical molecules linking chronic inflammation with cancer; its activity is meticulously regulated through various mechanisms (Dimitrakopoulos et al., 2020). NF-κB activates an array of target genes, such as those involved in proliferation and anti-apoptosis, and the crosstalk of NF-κB signaling influences numerous signaling pathways, including STAT3, AP1, interferon regulatory factors, NRF2, Notch, WNT-β-catenin, and p53 (W. Chen et al., 2011). NF-kB assumes a crucial role in cigarette smoke-induced carcinogenesis and encompasses a family of significant transcription factors (Rel proteins) characterized by structural similarities. This family is composed of five members: NF-kB1 (p105/p50), NF-kB2 (p100/p52), RelA (p65), RelB, and c-Rel (W. Chen et al., 2011). NF-κB p65 is a transcription factor that is highly expressed in cancerous tissues. In lung adenocarcinoma and squamous cell carcinomas, NF-κB activation induced by tobacco smoke modulates the expression of downstream pathways, such as COX-2, cyclin D1, and matrix metalloproteinase-9, thereby fostering cancer cell proliferation and survival (L. Zhang et al., 2023). NF-κB p65 is activated by a variety of cytokines, including IL-8, IL-6, TNFα, among others. In addition to regulating several canonical pro-growth genes, NF-κB p65 is also recognized for mediating PD-L1 mRNA levels across diverse cancer types (Ashrafi et al., 2022). Research has elucidated that the in vivo expression of chemokines, specifically IL-8/CXC ligands CXCL8 and CXCL5, is regulated by COX-2 in non-small cell lung carcinoma (NSCLC) (Rasmi et al., 2020; Yuan et al., 2000).

A. Development of Alternative Therapies for Lung Cancer Using GBE1 Inhibition

In conjunction with glycolysis, the aforementioned analysis implies that the suppression of glycogenesis may attenuate neoplastic proliferation. Hypoxic

environments within neoplastic cells frequently induce resistance to therapeutic interventions including radiotherapy, chemotherapy, and immunotherapy (Ashrafi et al., 2022). The expression of GBE1 confers protection to cells under hypoxic conditions, thereby facilitating energy acquisition from glycogen reserves, which is critical for both local proliferation and metastatic processes (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022). Moreover, GBE1 expression exhibits a significant correlation with the expression of various disease biomarkers such as survivin, TP53, VEGF, EGFR, and ALK mutations (L. Li et al., 2020). The inhibition of GBE1 presents a compelling approach for supplementary therapeutic strategies in the context of hypoxic cancer cell environments (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022).

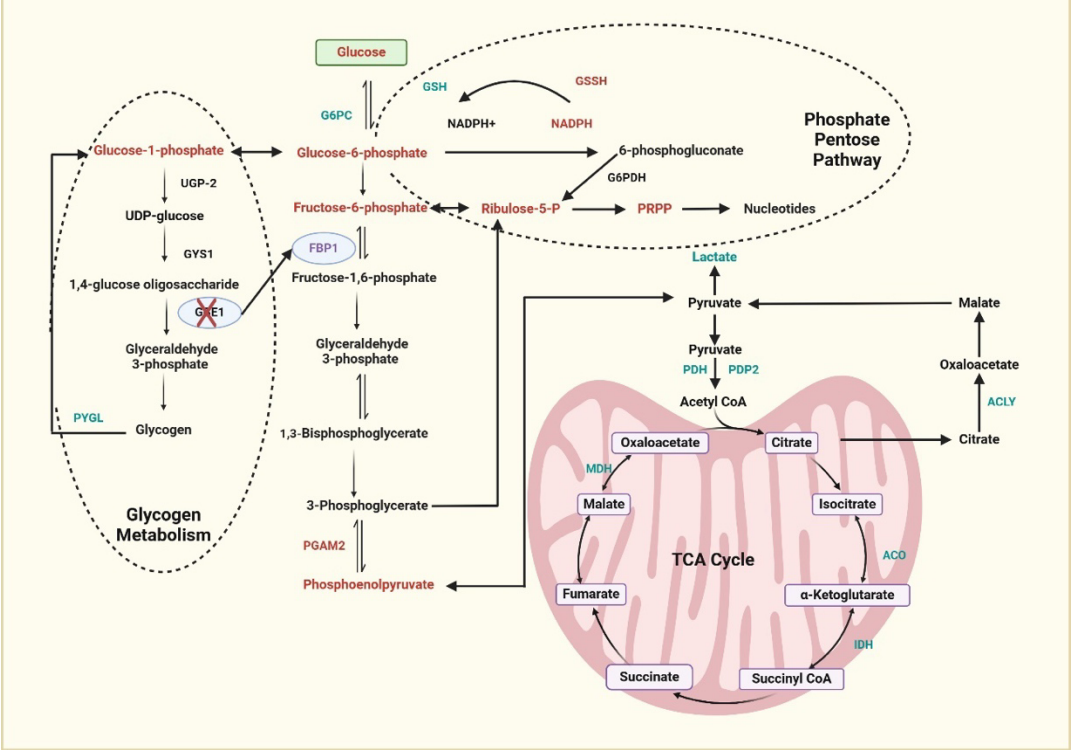


Figure 2. Alteration of Metabolic Signaling Pathway Mechanism by GBE1 Inhibition in Lung Cancer

Blocking GBE1 leads to induced FBP1 expression, which is critical for the glycolysis and PPP pathways. Figure created with https://BioRender.com (accessed on 16 December 2024).

GBE1 inhibition has been demonstrated to elevate the expression of FBP1, which is concomitant with a reduction in the methylation of the FBP1 promoter. An analytical study was conducted to validate this observation, employing whole-genome DNA methylation profiling techniques. The findings of this investigation identified a distinct CpG island, referred to as CGI, typically localized in proximity to FBP1 exon 1. Subsequently, bisulfite sequencing of the genome was performed on A549 cells to assess the methylation status of the FBP1 CpG island; the results indicated the presence of hypermethylation within these A549 cells. Furthermore, sequencing was conducted on the CpG-rich regions adjacent to the FBP1 transcription initiation site. Additionally, a targeted methylation analysis was executed utilizing methylation-specific PCR (MSP), which is designed to detect methylated alleles. Notably, the CpG island within FBP1 exhibited partial demethylation following treatment with the methyltransferase inhibitor

decitabine (5μM). A549 cells underwent a treatment regimen with decitabine for a duration of three days, resulting in a substantial increase in FBP1 expression at both the mRNA and protein levels (L. Li et al., 2019, 2020).

The inhibition of GBE1 has been elucidated to hinder the hypermethylation of the FBP1 promoter, thereby facilitating an increase in FBP1 expression, which is instrumental in the inhibition of tumorigenesis. The occurrence of GBE1 inhibition instigates a metabolic reprogramming process wherein glycogen is degraded by glycogen phosphorylase into glucose-1-phosphate. The blockade of GBE1 is also correlated with elevated reactive oxygen species (ROS) levels and diminished cell proliferation, culminating in the activation of the pentose phosphate pathway (PPP), which is adversely affected by the impaired glycogen metabolism. The elevation of ROS alongside the reduction in proliferation disrupts the survival mechanisms of cancer cells, ultimately leading to their demise. Prior research has substantiated that the inhibition of GBE1 significantly suppresses cellular proliferation, colony formation, cell migration, cell invasion, angiogenesis, tumor growth, metastasis, and enhances apoptotic processes (Zhen Chen et al., 2023; L. Li et al., 2019, 2020; Liang et al., 2022). (Figure 2).

A pharmacological agent that may serve as a therapeutic intervention is Flavopiridol, which has been shown to diminish GBE1 activity and impede neoplastic growth. The findings of the study indicated that Flavopiridol is capable of inhibiting various CDK-dependent kinases (L. Li et al., 2019, 2020). Furthermore, Flavopiridol has demonstrated an antitumor efficacy by promoting apoptosis, attenuating angiogenesis, and inhibiting glycogen phosphorylase, which in turn reduces glucose availability for glycolysis in both in vitro and in vivo experimental settings. Importantly, Flavopiridol has been found to exert no detrimental effects on normal physiological organs, such as the liver and kidneys (L. Li et al., 2020).

The inhibition of GBE1 via Flavopiridol has been demonstrated to decrease GBE1 enzymatic activity and impede the progression of cancer. Prior investigations have employed in vitro assays to assess GBE1 functionality. Flavopiridol has been shown to diminish the proliferation of A549 cells in a dose-dependent fashion. Following administration, the expression of GBE1 induced by hypoxia in A549 cells was significantly reduced. Furthermore, treatment with Flavopiridol for a duration of 24 hours resulted in an increase in apoptotic activity and a decrease in clonal formation, cellular migration, and invasive capabilities (L. Li et al., 2019). To evaluate the efficacy of Flavopiridol in inhibiting tumorigenesis in vivo, a xenograft mouse model was utilized. Three days subsequent to cell inoculation, the mice were randomly allocated into two cohorts, receiving either Flavopiridol or dimethyl sulfoxide (DMSO) as a control for a period of 41 days. In comparison to control subjects, it was observed that tumor growth in the Flavopiridol-treated mice was significantly suppressed, with both tumor volume and weight markedly diminished. Subsequent analysis of the xenografts revealed that GBE1 expression, as assessed by immunohistochemistry and western blotting, was drastically lower in the Flavopiridol-treated group relative to the control group (L. Li et al., 2020). The potential of combination therapy involving anti-PDL-1 immunotherapy alongside targeted therapy through GBE1 inhibition presents a promising avenue for future research (L. Li et al., 2019, 2020).

Conclusion

Currently, lung cancer treatments such as surgery, chemotherapy, radiation, immunotherapy, and targeted therapy have been developed. However, the survival rate is still less than 20% in 5 years. This disrupts the quality of life of lung cancer patients which hurts social and family life, as well as high and long-lasting treatment costs. In addition, hypoxic conditions in cancer cells often cause resistance to treatments such as radiotherapy, chemotherapy, and immunotherapy. GBE1 expression protects cells from hypoxia which allows cells to survive for local proliferation and metastasis. GBE1 inhibition is an attractive strategy for alternative therapy in hypoxic cancer cell conditions. Blockade of GBE1 prevents hypermethylation of the FBP1 promoter thereby preventing the Warburg effect and glycogen accumulation. GBE1 inhibition has also been shown to suppress proliferation, clone formation, cell migration, cell invasion, angiogenesis, tumor growth, metastasis, and increased apoptosis. Combination therapy between anti-PDL-1 immunotherapy and targeted therapy with GBE1 inhibition may be promising. On the other hand, a new innovation in developing lung cancer treatment management with the GBE1 gene therapy method, using the GBE1 gene mutation L224P and Y329S which is expected to inhibit GBE1 expression.

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