

Review

Phosphoglycerate Kinase 1: An Effective Therapeutic Target in Cancer

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Academic Editor: Sukmook Lee

Submitted: 27 November 2023 Revised: 2 January 2024 Accepted: 23 January 2024 Published: 6 March 2024

Abstract

Phosphoglycerate kinase 1 (PGK1) serves as a pivotal enzyme in the cellular glycolysis pathway, facilitating adenosine-triphosphate (ATP) production in tumor cells and driving the Warburg effect. PGK1 generates ATP through the reversible phosphorylation reaction of 1,3-bisphosphoglycerate (1,3-BPG) to Mg-adenosine-5'-diphosphate (Mg-ADP). In addition to its role in regulating cellular metabolism, PGK1 plays a pivotal role in autophagy induction, regulation of the tricarboxylic acid cycle (TCA), and various mechanisms including tumor cell drug resistance, and so on. Given its multifaceted functions within cells, the involvement of PGK1 in many types of cancer, including breast cancer, astrocytoma, metastatic colon cancer, and pancreatic ductal adenocarcinoma, is intricate. Notably, PGK1 can function as an intracellular protein kinase to coordinate tumor growth, migration, and invasion via posttranslational modifications (PTMs). Furthermore, elevated expression levels of PGK1 have been observed in cancer tissues, indicating its association with unfavorable treatment outcomes and prognosis. This review provides a comprehensive summary of PGK1's expression pattern, structural features, functional properties, involvement in PTMs, and interaction with tumors. Additionally highlighted are the prospects for developing and applying related inhibitors that confirm the indispensable value of PGK1 in tumor progression.

Keywords: PGK; protein kinase; glycolysis; post-translational modifications; cancer; small molecule inhibitor

1. Introduction

Phosphoglycerate kinase (PGK) family is a pivotal enzyme involved in the glycolytic pathway, known as the Embden-Meyerhof-Parnas pathway, responsible for catalyzing the conversion of glucose (or fructose) into pyruvate [1,2]. In the human genome, two distinct isoforms of glycerol phosphate kinase have been identified: PGK1 and PGK2 [3]. While PGK2 is an autosomal gene that exhibits tissue-specific expression during late spermatogenesis [4], PGK1 is expressed in all somatic cells and germ cells prior to meiosis as an X-linked gene [4].

In the human PGK1 protein structure, characterized by an open conformation (Protein Data Bank (PDB) code: 2xe7) [5], closed conformations (PDB codes: 2ZGV) [6] and complexes with transition state analogs of the closed conformation (PDB code: 2WZB) [7] as well as inhibitors (PDB codes: 4o33, 4o3f) [8], PGK1 functions as a monomeric enzyme composed of 417 amino acids. It comprises two distinct alpha helix structures that form domains of equal size, interconnected through hinge regions at the N- and C-termini. The N-terminal domain interacts with either phosphoglycerate (PG) or combined substrates, while the C-terminal domain binds to Mg-adenosine-5'-diphosphate

(Mg-ADP) or Mg-ATP. During the catalytic cycle, four hinge points facilitate inter-domain movement, creating a flexible bend that positions catalytic residues correctly. At this transitional stage, both substrate types bind simultaneously triggering conformational rearrangement from a high-affinity substrate-bound form to an open state exposed to the external environment for ATP production (Fig. 1) [9].

PGK1 plays a pivotal role as the key enzyme in glycolysis within cellular metabolism, primarily providing energy through the reversible phosphate transfer reaction from 1,3-diphosphoglyceric acid (1,3-DPGA) to Mg-ADP in the form of ATP. This reaction results in the production of 3-phosphoglycerate (3-PG) and adenosine phosphate Mg-ATP when magnesium is present [5,10]. In cancer cell metabolism, PGK1 assumes a central position due to its preference for glycolysis as an ATP-producing pathway. Elevated levels of PGK1 expression have been consistently observed across various cancer types, thereby diminishing its prognostic value as a negative marker [11]. Glycolytic enzymes play a crucial role in the metabolic reprogramming of cancer cells by facilitating increased biosynthesis demand through alternative sugar fermentation pathways [12]. Possessing oncogenic characteristics similar



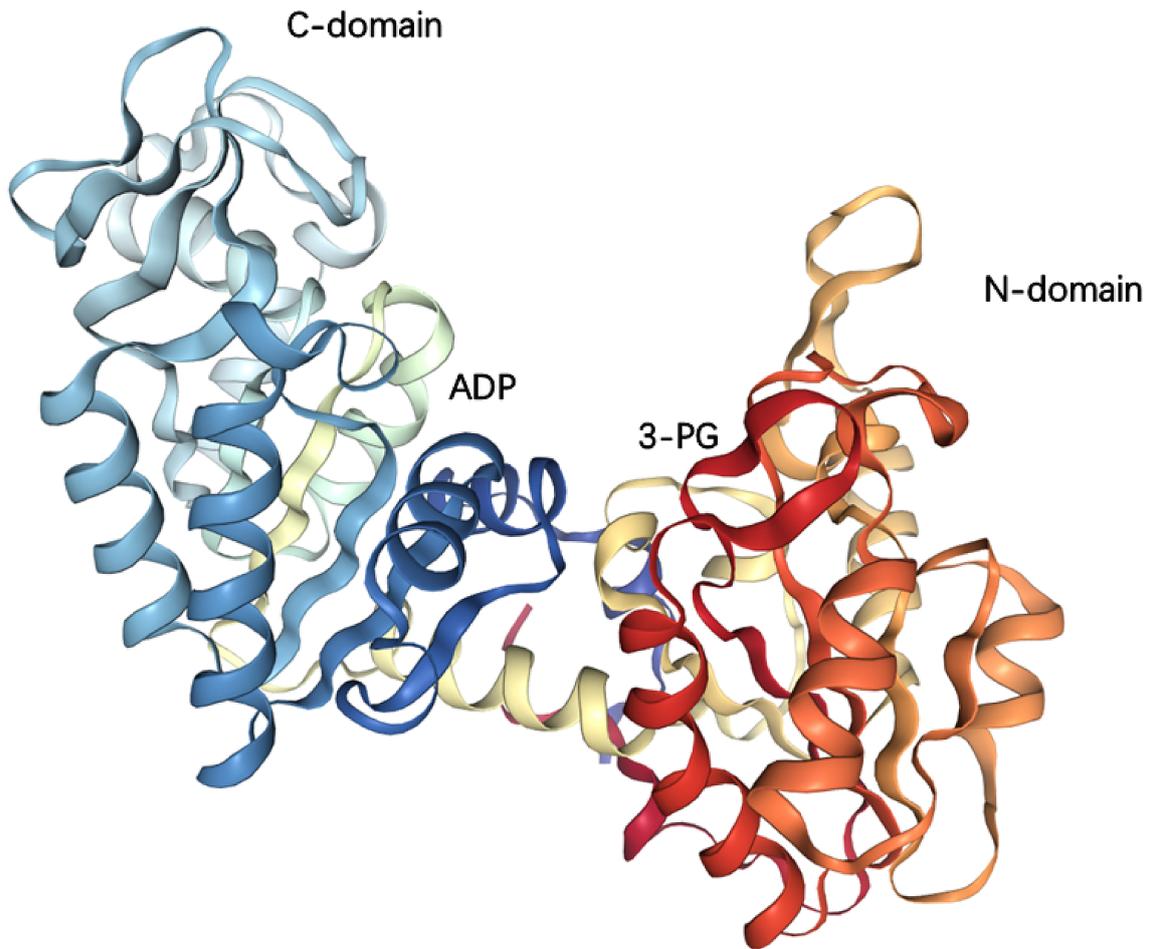


Fig. 1. The structure of phosphoglycerate kinase 1 (PGK1). Structure of data obtained from the Human Protein Atlas (HPA) (image available from <https://www.proteinatlas.org/>). ADP, adenosine-5'-diphosphate; 3-PG, 3-phosphoglycerate.

to many other genes associated with tumor progression, PGK1 promotes the proliferation, migration, and invasion of tumor cells. Consequently, targeting PGK1 has emerged as an essential molecular approach for tumor therapy and has gained significant research attention recently [13,14]. However, despite these advancements, much remains unknown regarding the fundamental aspects of PGK1. Although inhibitors targeting PGK1 have been developed, there is currently a lack of successful clinical drugs specifically designed to target this enzyme. Given the escalating incidence of cancer cases necessitating urgent clinical diagnosis, it is imperative to conduct research on small molecule targeted therapies against PGK1.

Therefore, in this study, we comprehensively explore the involvement of PGK1 in growth regulation while also investigating its role in promoting proliferation, and migration, invasion, and predicting poor prognosis across various common malignant tumors, to provide potential therapeutic solutions.

2. The Role of PGK1 in Tumor Cells

Hypoxia is a crucial characteristic of cancer, leading to metabolic reprogramming from oxidative phosphorylation to glycolysis in cancer cells when deprived of oxygen [15–17]. Metabolic reprogramming has emerged as a hallmark of cancer biology [18–20]. However, even under sufficient oxygen supply, malignant tumor cells exhibit abnormal energy metabolism known as the Warburg effect, where glycolysis is also activated [21–23]. Unlike normal cells, most cancer cells maintain a high rate of glycolysis and produce lactic acid for energy production despite the presence of oxygen [24,25]. PGK1 plays an essential role in ATP production within the glycolytic pathway [26], catalyzing the conversion of 1,3-diphosphoglycerate into ADP and generating 3-phosphoglyceric acid and ATP. Consequently, PGK1 promotes the metabolic activity of cancer cells [13,27].

To investigate the association between PGK1 expression level and human cancer prognosis, we conducted a comprehensive analysis of data from multiple online databases, including differential gene expression analy-

sis in Tumor, Normal, and Metastatic tissues (TNMplot) (<https://tnmplot.com/>), Human Protein Atlas (HPA) (<https://www.proteinatlas.org/>), and Kaplan-Meier Plotter database (<https://kmplot.com/>). TNMplot encompasses 56,938 unique samples derived from Gene Expression Omnibus database (GEO), Genotype-Tissue Expression (GTEx), The Cancer Genome Atlas (TCGA), and Therapeutically Applicable Research To Generate Effective Treatments databases (TARGET), consisting of 15,648 normal samples, 40,442 tumor samples, and 848 metastatic samples. The Kaplan Meier Plotter enables evaluation of the correlation between gene expression (mRNA, miRNA protein and DNA) and survival in over 35k samples across 21 tumor types using statistical tools such as Cox proportional hazard regression and error detection rate calculation. Moreover, KM Plotter performs approximately 18k analyses daily making it widely utilized worldwide for identification and validation of survival biomarkers. On the other hand, HPA resources provide an extensive immunohistochemical-based protein expression profile encompassing normal tissues, cancer samples, and cell lines with more than five million immunohistochemical staining images generated at 708 points. Furthermore, the HPA has analyzed about one-fourth of the human genome utilizing a panel of 6122 antibodies targeting 5011 human proteins [28].

As depicted in Fig. 2, analysis of the TNMplot database revealed that among the 22 examined organs, only the esophagus and thyroid exhibited no significant difference in expression between the normal and tumor groups. Conversely, the remaining 20 organs displayed substantial differences (Fig. 2A). Consequently, heightened PGK1 expression was associated with these 20 tumors. To further validate this association, data from the Kaplan-Meier Plotter database confirmed a noteworthy inverse correlation between high PGK1 expression and tumor prognosis (Fig. 2B). Notably, within the myeloma cancer group, patients with elevated PGK1 expression experienced significantly shorter overall survival compared to those with low expression; some data even indicated an average overall survival of approximately 100 days [13,29–33]. Analysis results from the HPA database additionally substantiated increased PGK1 expression in other suspected malignant tumors such as colorectal cancer, lung cancer, kidney cancer, breast cancer and prostate cancer (Fig. 2C). Furthermore, relevant studies have provided supplementary evidence regarding elevated levels of PGK1 protein in breast cancer [34], astrocytoma [35], metastatic colon cancer [29], and pancreatic ductal adenocarcinoma [36]. Additionally, increased mRNA levels of PGK1 have been observed in various types of cancers [37].

Based on information obtained from multiple databases, *PGK1* gene exhibit high expression levels in various tumors, with a negative correlation observed between their expression status and tumor prognosis. This

suggests a strong association between *PGK1* and diverse cancer types. Consequently, given the escalating incidence of cancer, it is imperative to investigate the pivotal role of *PGK1* in the growth, proliferation, migration, invasion, and prognostic prediction of common malignant tumors. The objective of this study is to provide potential therapeutic strategies for combating malignant tumors.

3. PTMs of PGK1 in Cancer

PGK1 is a monomeric enzyme comprising two equally sized alpha helix domains connected as a central structure [1,9]. The ligand binding domain is situated between these two α -helical domains [38,39]. The primary function of PGK1 involves transferring phosphate groups from 1,3-diphosphoglyceric acid (1,3-BPG) to ADP to generate 3-phosphoglyceric acid (3-PG) and ATP [40]. Previous studies have identified three conformational states of PGK1 upon substrate binding: an open state in the absence of substrate, a semi-open state following interaction with 1,3-BPG, and a closed state subsequent to binding with ADP and 1,3-BPG [40]. The analysis of PGK1 structure in the Uniprot database is depicted in Fig. 3A, revealing a total of 417 amino acids encompassing 9 domains and sites, along with 41 Protein post-translational modifications (PTMs) (including modified residue 23 and modified residue large scale data 18), 2 sequence information, and 48 structural features (comprising Helix 24, Beta strand 21, and three turns). The distribution of domains and sites is uniform throughout the protein sequence, while PTMs are predominantly concentrated within the first two hundred amino acids. Notably, the predominant structural feature observed is helical conformation.

PTMs of PGK1 in tumor cells play a crucial role in regulating tumor metabolism and growth, highlighting their significance as potential therapeutic targets (Table 1, Ref. [26,30,39,41–47]).

3.1 Phosphorylation of PGK1

According to relevant studies, polarized M2 macrophages have been shown to secrete interleukin-6 (IL-6) and facilitate the phosphorylation of PGK1-threonine (T) 243 in tumor cells through the activation of 3-phosphoinositol-dependent protein kinase 1 (PDK1). In one study, this phosphorylation event was found to enhance PGK1-catalyzed glycolysis by modulating substrate affinity, thereby promoting tumor cell metabolism and facilitating the proliferation and development of glioblastoma multiforme (Fig. 3B) [41].

In the context of glioblastoma, Yajuan Zhang and colleagues [41] made an interesting discovery regarding the interaction between PTEN (a tumor suppressor phosphatase) and PGK1. They found that PTEN's protein phosphatase activity has a direct effect on PGK1, specifically at position 324 where it dephosphorylates and autophosphorylates PGK1 (tyrosine). This interaction ultimately leads to the

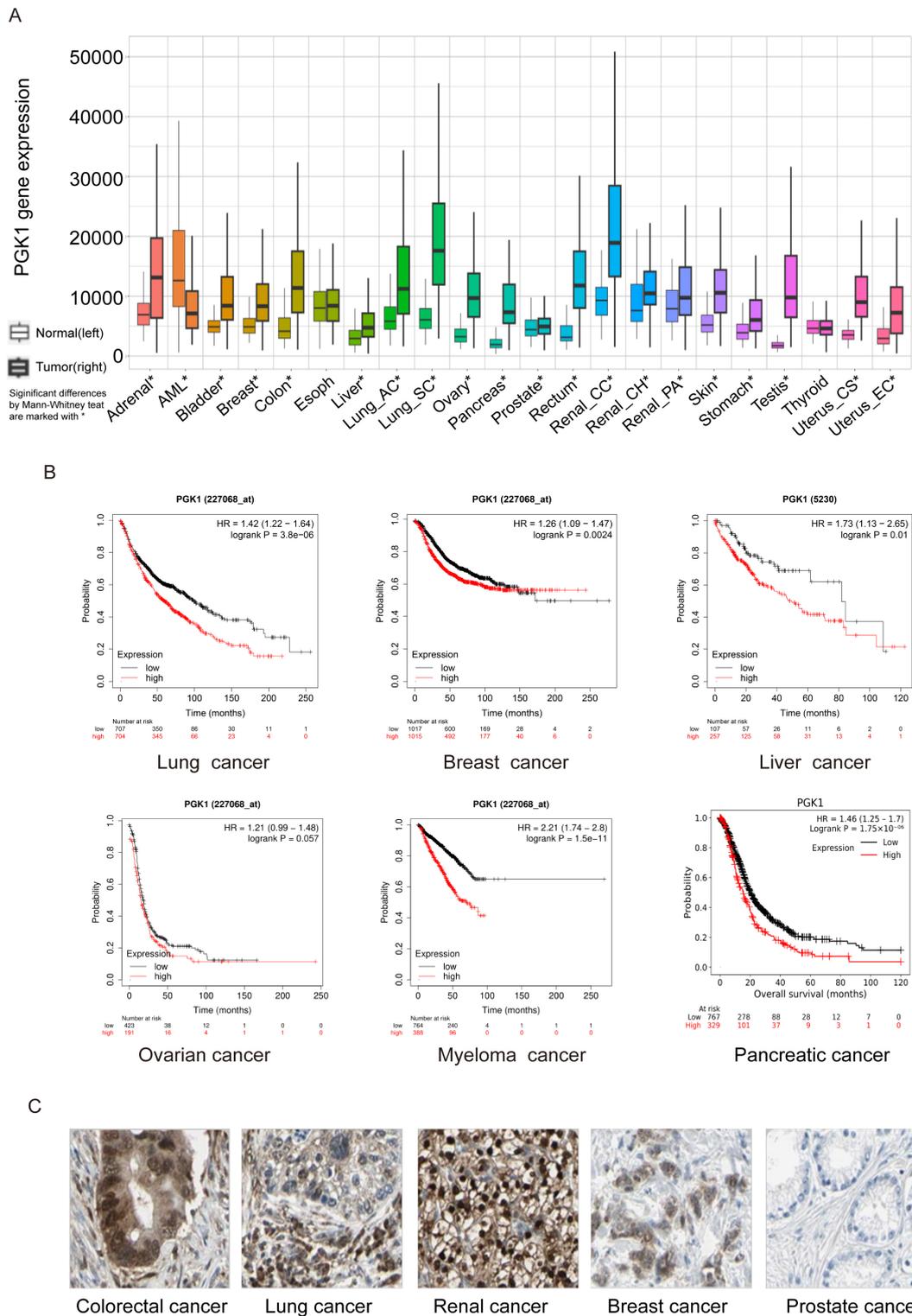


Fig. 2. Bioinformatic analyses of the expression and prognosis of PGK1 in cancer. (A) The expression of PGK1 in normal and tumor was assessed using the TNMplot database (<https://tnmplot.com/>). (B) The relationship between the expression of PGK1 and the survival time of cancer patients was assessed using the Kaplan-Meier Plotter online database (<https://kmplot.com/>). High PGK1 expression predicts poor survival in lung cancer, breast cancer, liver cancer, ovarian cancer, myeloma cancer, and pancreatic cancer. (C) Immunohistochemical results of PGK1 using the HPA 23.0 online database (<https://www.proteinatlas.org/>) in tissues of colorectal cancer, lung cancer, renal cancer, breast cancer, and prostate cancer. TNMplot, Tumor, Normal, and Metastatic tissues; AML, acute myeloid leukemia; AC, adenocarcinoma; SC, squamous cell carcinoma; CC, cell carcinoma; CH, chromophobe; PA, papillary carcinoma; CS, carcinosarcoma; EC, endometrial.

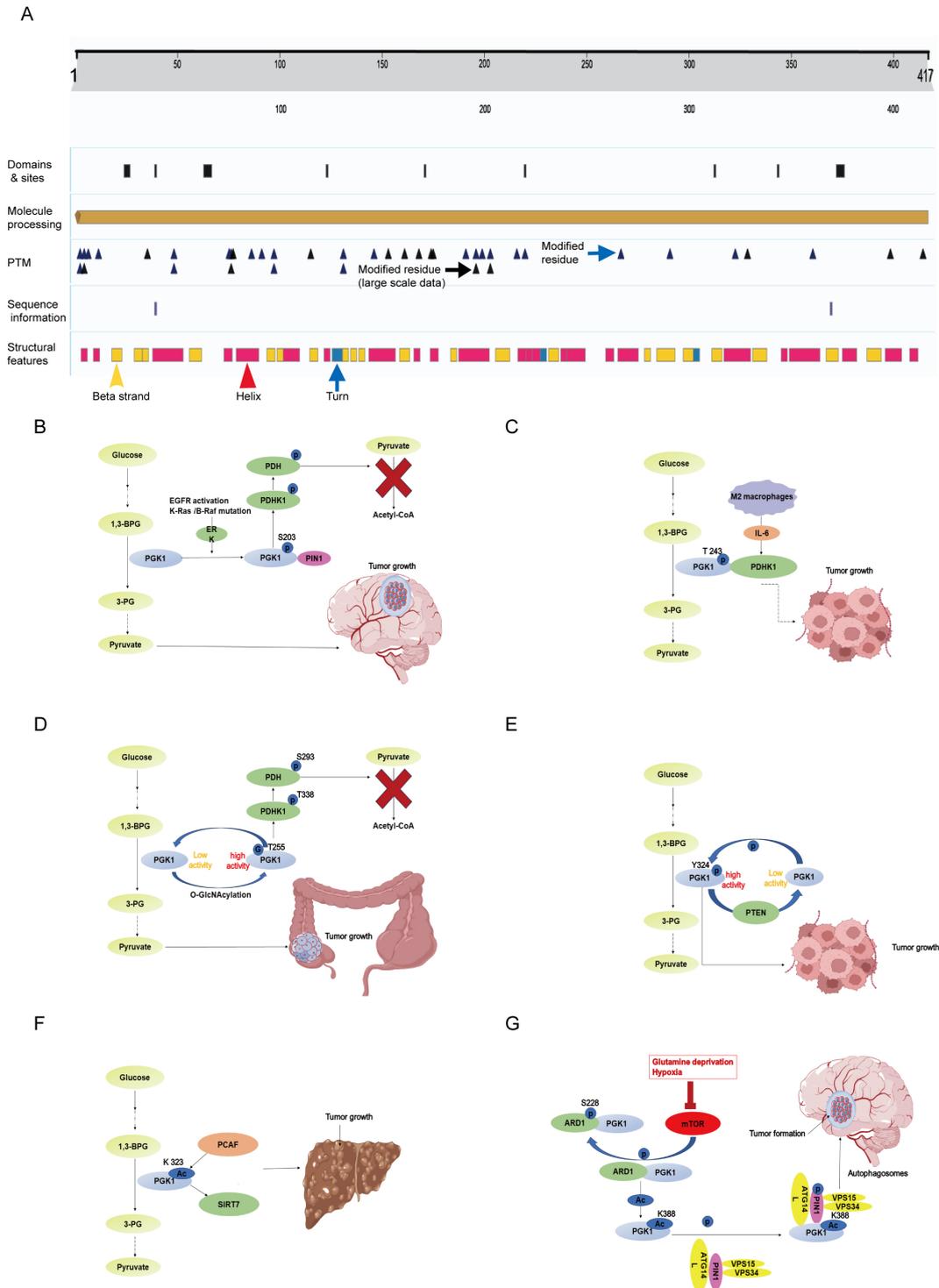


Fig. 3. Amino acid sequence and posttranslational modifications of PGK1. (A) The amino acid sequence of PGK1 was obtained from the Uniprot database (<https://www.uniprot.org/>). (B) Phosphorylation of T243 occurs on PGK1. (C) Phosphorylation of Y324 is detected on PGK1. (D) Phosphorylation of S203 occurs on PGK1. (E) Acetylation of K388 takes place on PGK1. (F) Acetylation of K323 is observed on PGK1. (G) O-GlcNAcylation of T255 is observed on PGK1. PTM, post-translational modifications; 1,3-BPG, 1,3-diphosphoglyceric acid; 3-PG, 3-phosphoglyceric acid; IL-6, interleukin-6; PDHK1, dependent protein kinase 1; PTEN, a tumor suppressor phosphatase; EGFR, epidermal growth factor receptor; PDH, Pyruvate dehydrogenase; PIN1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; ARD1, Arrest Defective 1; Ac, O-linked N-acetylglucosamine; mTOR, Mechanistic target of rapamycin; K388, lysine 388; S228, serine 228; P, phosphorylate; VPS, ventriculoperitoneal shunt; ATG14L, pre-autophagosome/autophagosome marker; K323, lysine 323; PCAF, P300/CBP associated factor; SIRT7, Sirtuin 7; T255, threonine 255; T338, threonine 255; S293, serine 293.

Table 1. Posttranslational modifications of PGK1.

PTM	Sites	Reference	Cancer research	Mechanisms of research
Phosphorylation	(1) T243	(1) [41]	(1) Glioblastoma multiforme	(1) Polarized M2 macrophages have been shown to secrete IL-6 and facilitate the phosphorylation of PGK1 T243 in tumor cells through the activation of PDPK1.
	(2) Y324	(2) [42]	(2) Glioblastoma	(2) PTEN Suppresses Glycolysis by Dephosphorylating and Inhibiting Autophosphorylated PGK1 Y324.
	(3) S203	(3) [26,43]	(3) Breast cancers, Glioblastoma, Liver cancers, Lung cancers, Stomach cancers, Esophageal cancers, and Brain tumor	(3) ERK-dependent phosphorylation of PGK1-S203, followed by Pin1-mediated cis-trans isomerization and subsequent binding of PGK1 to the TOM complex. This facilitates translocation of PGK1 to mitochondria. Once inside the mitochondria, PGK1 directly interacts with PDHK1 at T338 and phosphorylates it. This phosphorylation enhances PDHK1 activity and PDHK1-mediated PDH phosphorylation.
Acetylation	(1) K388	(1) [39]	(1) Brain tumor	(1) The induction of autophagy that is crucial for brain tumor formation relies on ARD1-dependent PGK1 K388 acetylation caused by glutamine deficiency and hypoxia, along with PGK1-mediated Beclin1 S30 phosphorylation.
	(2) K323	(2) [30]	(2) Liver cancer	(2) P300/PCAF and Sirtuin 7 (SIRT7) as key regulators responsible for inhibiting PGK1 K323 acetylation resulted in significant inhibition of glycolysis, proliferation, and tumorigenesis in mouse xenotransplantation models used to simulate liver cancer progression.
glycosylation modification	(1) T255	(1) [44]	(1) Colon cancer	(1) PGK1 T255 can be dynamically and reversibly modified by O-GlcNAc, to enhances the production of lactate and facilitates its movement into mitochondria. Once inside the mitochondria, PGK1 hinders the PDH complex to reduce oxidative phosphorylation.
Ubiquitination	—	(1) [45]	(1) Non-small cell lung cancer	(1) The interaction between lncRNA MetaLnc9 and PGK1 which helps mitigate PGK1 ubiquitination.
	—	(2) [46]	(2) Gallbladder cancer	(2) The interaction between GBCDRlnc1 and PGK1 which helps mitigate PGK1 ubiquitination.
	—	(3) [47]	(3) Pancreatic cancer	(3) KIF15 enhances the glycolysis ability of PC by recruiting USP10 and PGK1, and the KIF15/USP10/PGK1 axis may be an effective treatment for PC.

ERK, extracellular signal-regulated kinase; TOM, the translocase of outer mitochondria; PDPK1, 3-phosphoinositol-dependent protein kinase 1.

inhibition of glycolysis, ATP production, and proliferation in brain tumor cells. Moreover, when they introduced mutant forms of PGK1 with a specific alteration at position 324 (PGK1Y324F), they observed suppression of the formation of brain tumors. Additionally, their analysis of human glioblastoma samples revealed an interesting correlation: lower levels of phosphorylation at position 324 in PGK1 were associated with higher expression levels of PTEN and better prognosis for glioblastoma patients (Fig. 3C) [42].

In a study conducted by Shao *et al.* [43], the phosphorylation levels of PGK1 serine (S) 203 were analyzed in 818 different cases of cancer. The results revealed that tumor tissues, across all five types of cancer, exhibited higher levels of PGK1 S203 phosphorylation compared to their corresponding normal tissues. Moreover, an association was found between elevated levels of PGK1 S203 phosphorylation and shorter overall survival rates in breast, liver, lung, stomach, and esophageal cancers. Additionally, increased expression of PGK1 S203 phosphorylation was observed in advanced tumor Node Metastasis (TNM) staging for breast and esophageal cancers. Independent prognostic significance for shorter overall survival was also demonstrated by PGK1 S203 phosphorylation in liver, lung, and gastric cancers [43].

Coincidentally, the researchers investigating PGK1 S203 also took into consideration the findings of Li *et al.* [26]. It was demonstrated by Xinjian Li and his colleagues [26] that in brain tumor development, hypoxia, EGFR activation, K-Ras G12V, and B-Raf V600E expression can induce the translocation of phosphoglycerate kinase 1 (PGK1) to mitochondria. The primary mechanism involves extracellular signal-regulated kinase (ERK)-dependent phosphorylation of PGK1 S203, followed by Pin1-mediated cis-trans isomerization and subsequent binding of PGK1 to the TOM complex. This facilitates successful translocation of PGK1 to mitochondria. Once inside the mitochondria, PGK1 directly interacts with PDHK1 at T338 and phosphorylates it. This phosphorylation enhances PDHK1 activity and PDHK1-mediated PDH phosphorylation. Consequently, pyruvate utilization through PDH is inhibited while cytoplasmic production of pyruvate and lactic acid increases within the mitochondria. These metabolic changes promote cell proliferation and tumorigenesis. Furthermore, Li *et al.*'s [26] study revealed a significant correlation between phosphorylation of PGK1 S203 and poor prognosis in patients with glioblastoma (Fig. 3D).

3.2 Acetylation of PGK1

Glutamine deprivation and hypoxia have been recognized as triggers of autophagy in various cancer cells, playing a vital role in maintaining cellular equilibrium, including cell metabolism [48]. Xu *et al.* [39] demonstrated that when glutamine is scarce and oxygen levels are low, the inhibition of Arrest Defective 1 (ARD1) S228 phosphorylation by mTOR occurs. This leads to the association

between ARD1 and PGK1, resulting in the acetylation of PGK1 K388. Acetylated PGK1 can directly interact with Beclin1. Experimental evidence has confirmed that the induction of autophagy that is crucial for brain tumor formation relies on ARD1-dependent PGK1 acetylation caused by glutamine deficiency and hypoxia, along with PGK1-mediated Beclin 1 S30 phosphorylation (Fig. 3E) [39].

In liver cancer samples and cell lines, a study conducted by Hu *et al.* [30] revealed a notable upregulation of PGK1 expression, which showed an inverse correlation with patient survival and overall expression levels. The researchers identified P300/CBP associated factor (PCAF) and Sirtuin 7 (SIRT7) as key regulators responsible for the acetylation of PGK1 at lysine (K)323. PCAF and SIRT7 inhibit PGK1 K323 acetylation resulted in significant inhibition of glycolysis, proliferation, and tumorigenesis in mouse xenotransplantation models used to simulate liver cancer progression (Fig. 3F) [30].

3.3 PGK1 Glycosylation Modification

In addition to phosphorylation and acetylation, PGK1 can undergo O-GlcNAc modification, which is a significant type of post-translational modification. Nie *et al.* [44] demonstrated that the enzyme PGK1, responsible for producing ATP in glycolysis, can be dynamically and reversibly modified at threonine 255 (T255) by O-linked N-acetylglucosamine (O-GlcNAc). This specific modification of PGK1 with O-GlcNAcylation enhances the production of lactate and facilitates its movement into mitochondria. Once inside the mitochondria, PGK1 hinders the pyruvate dehydrogenase (PDH) complex to reduce oxidative phosphorylation. Moreover, through a xenotransplantation model experiment, it was confirmed that T255 O-GlcNAcylation of PGK1 stimulates proliferation and glycolysis in colon cancer cells, ultimately promoting tumor growth (Fig. 3G) [44].

3.4 Ubiquitination of PGK1

Ubiquitination of PGK1 has become a prominent area of investigation in the field of tumor research. Recent studies have revealed that the protein kinase activity of PGK1 is intricately linked to the activation of autophagy [39,49]. Additionally, researchers from Tao Yu's team reported on the interaction between LINC00963 long coding RNA (lncRNA MetaLnc9) and PGK1 by RNA Immunoprecipitation (RIP) technology, which helps mitigate its ubiquitination in non-small cell lung cancer [45]. Moreover, Cai *et al.* [46] expanded upon this knowledge by demonstrating that an lncRNA called gallbladder cancer drug resistance-associated lncRNA1 (GBCDRlnc1) directly interacts with PGK1. This interaction leads to an increase in PGK1 protein levels by inhibiting its ubiquitination process. However, GBCDRlnc1 has also been shown by Cai *et al.* [46] to promote autophagy in gallbladder cancer cells and ultimately contribute to drug resistance. Therefore, it

can be concluded that lncRNA GBCDRlnc1 induces autophagy and confers drug resistance in gallbladder cancer cells through its interaction with PGK1, preventing degradation [46].

Glycolysis represents a pivotal metabolic reprogramming event in pancreatic cancer (PC). In an unprecedented discovery, the research team led by Gang Quan has unveiled that KIF15 actively promotes the glycolytic capacity of PC cells and facilitates the growth of PC tumors. Employing mass spectrometry (MS) and Co-IP assay techniques, it was demonstrated that KIF15 effectively recruits and enhances the interaction between PGK1 and USP10. Furthermore, through ubiquitination assays, it was confirmed that KIF15 plays a crucial role in recruiting USP10 to exert its deubiquitinating effect on PGK1. This groundbreaking study provides compelling evidence for the first time that KIF15 augments PC glycolysis by orchestrating the recruitment of USP10 and PGK1, thereby highlighting the potential therapeutic significance of targeting the KIF15/USP10/PGK1 axis in treating PC [47].

4. Clinical Significance of PGK1 in Many Types of Tumors

4.1 Breast Cancer

Despite significant progress in early detection and treatment, breast cancer remains a prevalent form of malignancy among women based on the latest data from the American Cancer Society in 2023, with a consistent increase in new cases reported from 2015 to 2019 [50]. Breast cancer cells undergo a transformation that results in weakened cell-to-cell connections, which promotes the spread of cancer and increases its fatality rate [51,52].

PGK1 has been linked to the promotion of tumor growth [13,26,27]. Previous research has shown that PGK1 can increase lactate production in breast cancer cells and facilitate tumor growth [26]. Studies have revealed that NEAT1 induces breast tumor growth [53,54] and glycolysis [55–57] by binding directly with PGK1/PGAM1/ENO1 complexes, thus facilitating efficient substrate pathways for glycolysis [58]. Knockout of PGK expression inhibits the invasion of breast cancer cells and reverses the epithelial mesenchymal transition process while promoting the metastasis of breast cancer [59]. Hypoxia inhibits Long non-coding RNAs (lncRNAs) LINC00926 expression can also promote breast cancer metastasis [60]. Elevated levels of both PGK mRNA and promoter hypomethylation are associated with poor prognosis in breast cancer patients, particularly phosphorylation at S203 on PGK which is significantly correlated with shorter overall survival (OS) and advanced TNM staging [43]. Biogenic analysis shows upregulation of both mRNA and protein expression levels of PGK across various clinicopathological subtypes of breast cancer, highlighting its crucial role in proliferation, migration, and invasion processes within human breast cancer cells [61].

4.2 Liver Cancer

Liver cancer is ranked as the fifth most common malignancy globally and is the third leading cause of cancer-related death [62,63]. In liver cancer research, significant attention has been paid to PGK1. Overexpression of PGK1 has consistently been observed in clinical samples and cancer cell lines associated with liver cancer cases. Experimental evidence also demonstrates that reducing PGK1 levels decreases both the occurrence and growth of liver cancer cells [30]. Moreover, comprehensive analysis indicates that PGK1 acts as an independent prognostic factor for reduced overall survival in patients with liver cancer [43]. By promoting glycolysis and enhancing metabolic efficiency within human liver tumor tissues, PGK1 facilitates ATP production to support hepatic carcinoma growth. Additionally, increased lactic acid accumulation promotes metastasis and correlates with unfavorable prognosis and overall survival rates among patients diagnosed with this disease [64]. These findings collectively highlight the potential therapeutic significance of targeting PGK1 for the effective management of liver cancer.

In addition to its direct impact on liver cancer, Chen *et al.* [65] discovered that mcPGK1 (mitochondrial phosphoglycoside kinase 1 translocated circular RNA) has been found to have high expression levels in tumor initiating cells (TICs), apart from its direct impact on liver cancer. It facilitates the movement of PGK1 to the mitochondria through the translocase of outer mitochondria 40 (TOM40). Considering that mitochondrial structure and function can be influenced by various external factors such as hypoxia, starvation, infection, tumorigenesis, and different stages of the cell cycle regulating glycolysis and oxidative phosphorylation (OXPHOS) activity; G1 phase cells tend towards OXPHOS while S phase cells prefer glycolysis. By promoting the localization of PGK1 within mitochondria, mcPGK1 contributes to metabolic reprogramming from OXPHOS to glycolysis. Ultimately, this leads to inhibition of mitochondrial oxidative phosphorylation through reprogramming of the PGK1-PDK1-PDH axis, thereby promoting glycolysis and regulating tumorigenesis and development [65]. Interestingly, N6-methyladenosine (m6A) RNA methylation and its associated enzyme methyltransferase-like 3 (METTL3) can also boost the expression of PGK1 by upregulating m6A modification of nuclear factor of activated T-cells 5 (NFAT5). This ultimately leads to increased proliferation and metastasis [66]. Similarly, miR-450b-3p has an inhibitory effect on hepatocellular carcinoma (HCC) proliferation and cell division by inhibiting PGK1 expression in HCC cell lines [67]. PRAS40 is phosphorylated by PGK1 and mediates the inhibition of autophagy-mediated cell death, thereby promoting cell proliferation and ultimately promoting the occurrence and development of HCC [68]. In order to find highly sensitive and specific biomarkers for predicting HCC recurrence, Liu *et al.* [69] confirmed in a cohort study that high serum PGK1 levels were closely

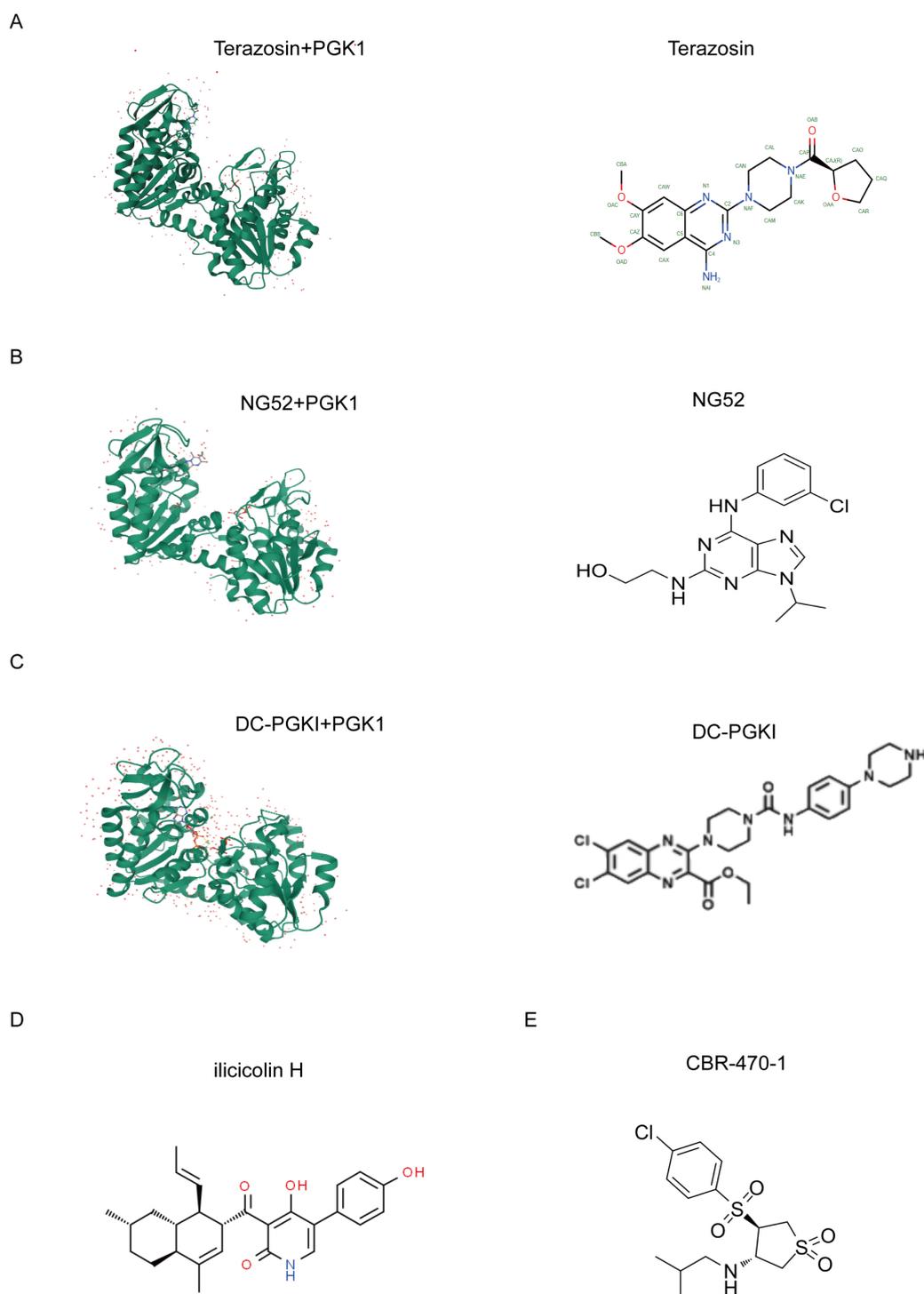


Fig. 4. The PGK1 binding complex with its inhibitor and the chemical structure of the inhibitor. (A) The PGK1 binding complex with Terazosin and the chemical structure of Terazosin (Protein Data Bank (PDB) database: <https://www.rcsb.org/>). (B) The PGK1 binding complex with NG52 and the chemical structure of NG52 (PDB database: <https://www.rcsb.org/>). (C) The PGK1 binding complex with DC-PGKI and the chemical structure of DC-PGKI (PDB database: <https://www.rcsb.org/>, and References [104]). (D) The chemical structure of ilicicolin H (Chemspider: <http://www.chemspider.com/>). (E) The chemical structure of CBR-470-1 (PDB database: <https://www.rcsb.org/>).

related to early HCC recurrence and poor prognosis, suggesting that PGK1 may be a new biomarker for the diagnosis of HCC.

4.3 Prostate Cancer

Prostate cancer (PCa) has emerged as the primary contributor to mortality among elderly males in both the United

States and Europe. In 2013, there were approximately 238,590 reported cases of PCa in the US, resulting in 29,720 fatalities [70], with nearly all deaths attributed to prostate cancer and its spread to the bones [71].

Liquid biopsy shows great potential in utilizing circulating tumor cells (CTCs) as important biomarkers for monitoring and predicting cancer outcomes. In relation to prostate cancer (PCa), researchers have identified PGK1 as a possible new marker [72]. A study conducted by Chen *et al.* [73] revealed that evaluating the metabolic marker (PGK1/G6PD) could provide insights into the functional activity of CTCs when compared to their morphological classification using EMT criteria. These findings indicate that examining the metabolic traits of CTCs, especially those with high metabolism like GM+CTCs, may offer valuable information about prostate cancer metastasis [73]. Additionally, research has indicated the significant impact of tumor-mesenchymal interactions in the tumor microenvironment on the development and progression of cancer. Through laser capture microdissection and cDNA microarray analysis, it was discovered that prostate tumor myofibroblasts or cancer-associated fibroblasts (CAFs) exhibited a notable increase in PGK1 expression. Experimental results demonstrated that overexpression of PGK1 in CAFs led to higher proliferation rates and enhanced ability to promote invasion of prostate tumor cells *in vitro*, potentially through upregulation of MMP-2 and MMP-3 expression as well as activation of the AKT and ERK pathways. Co-implantation of fibroblasts with elevated levels of pgk1 alongside prostate tumor cells facilitated accelerated growth of the tumor cells when tested *in vivo*. Overall, these findings suggest that PGK1 plays a supportive role by facilitating interactions between cancer cells and their surrounding microenvironment [74], or by regulating critical factors involved in triggering the angiogenesis required for tumor metastatic growth [75].

Prostate cancer (PCa) is a solid tumor that spreads to the bones. PGK1 in PCa cells stimulates the differentiation of bone marrow stromal cells into bone-forming cells, while the secreted PGK1 inhibits the formation of bone-destroying cells called osteoclasts. Experimental findings indicate that PGK1 released by PCa influences bone development at the metastatic site by promoting bone formation, suppressing osteoclastic activity, and inducing an osteogenic phenotype in PCa cells [76]. However, there is still limited understanding regarding the molecular mechanisms underlying the primary human skeletal characteristics associated with PCa disease. Furthermore, it remains unclear how PGK1 regulates mineralization; therefore, any interpretations made based on available experimental data should be considered speculative. It is plausible that PGK1 may impede osteoclast production through VEGF secretion inhibition. Increased expression of PGK1 has been strongly correlated with unfavorable prognosis among patients diagnosed with PCa [76].

4.4 Lung Cancer

Lung cancer is a highly prevalent form of cancer, accounting for 11.6% of all global cancer cases and being the leading cause of cancer-related deaths worldwide. It is estimated that around 2 million new cases and 1.76 million fatalities occur each year due to this disease, with over 1.7 million reported deaths in 2018 alone [77,78]. The most common histological subtype of lung cancer is non-small-cell lung cancer (NSCLC), which makes up approximately 85% of all diagnosed cases [79].

lncRNA play a crucial role in the development of lung cancer, specifically in its progression and the formation of tumors. The increased expression of LINC00963 (MetaLnc9) in human NSCLC samples is associated with a negative prognosis, as it promotes the migration and invasion of NSCLC cells both *in vitro* and *in vivo*. Research has shown that MetaLnc9 interacts with PGK1, preventing its degradation within NSCLC cells. This interaction activates the AKT/mTOR signaling pathway, which is known to contribute to carcinogenesis [45]. Clinically, high levels of PGK1 protein have been linked to survival outcomes for patients with non-small cell lung cancer, including overall survival and disease-free survival. Additionally, studies have found that PGK1 can induce lung cancer migration by directly binding HIV Tat-specific factor 1 [80]. In Lung Adenocarcinoma (LUAD), PGK1 modulates the immune microenvironment by influencing the crosstalk between tumor metabolism and immune editing within the tumor microenvironment (TME). These findings provide valuable insights into potential combination therapy strategies for Lung Adenocarcinoma (LUAD) that target immunometabolism; however, further experimental and clinical translational studies are needed [81].

4.5 Gliomas

Gliomas are most commonly observed in the central nervous system, which includes the brain and spinal cord. At present, the main treatment approaches for glioma involve removing the tumor through surgery, along with additional therapies such as chemoradiotherapy and targeted interventions [82,83].

In the case of glioma, cancer cells increase their glycolysis activity to store energy. PGK1 plays a crucial role in promoting tumor cell glycolysis and enhancing the proliferation of glioma cells [84]. Interestingly, high expression levels of PGK1 have been observed in radiation-resistant astrocytoma [33,35], suggesting its potential involvement as a biomarker for the radiation-resistant phenotype. Further investigations have shown that poor prognosis in glioblastoma patients is positively associated with phosphorylation levels of PGK1 at Y324 and S203 [26,42]. However, within the tumor microenvironment, polarized M2 macrophages secrete interleukin-6 (IL-6) to facilitate tumor cell phosphorylation of PGK1 at T243. This ultimately leads to enhanced proliferation and formation of

glioblastoma multiforme [41]. In terms of the autophagy mechanism, acetylation of PGK1 at K388 directly interacts with Beclin1 to initiate autophagy and further promote brain tumor development [39]. Additionally, secreted PGK1 contributes to the bystander effect observed during MicroRNA-10b (miR-10b) gene editing in gliomas [85]. Furthermore, NEAT1 specifically stabilizes PGK1 through interaction and promotes the progression of glioma [86]. Conversely, miR-6869-5p can inhibit the growth and invasion of glioma cells by binding to PGK1 and down regulating its expression [87]. Similarly, LHX9 and P7C3 bind to PGK1 resulting in down regulation at protein level and through total intracellular kinase activity; thereby inhibiting the malignant growth of glioma both *in vitro* and *in vivo* [88,89].

4.6 Colorectal Cancer

Colorectal carcinoma (CRC) stands out globally as one of the most commonly diagnosed malignant diseases and represents a major contributor to cancer-related fatalities with around 1.4 million fresh instances reported in 2012 alone resulting in almost 700,000 deaths. Projections indicate an alarming rise in CRC incidence with an estimated surge to about 2.5 million new cases anticipated by the year 2035 [90,91]. Within colon carcinomas there exists a notable escalation in PGK1 expression throughout the transition from adenomas to carcinomas [92], thus actively promoting tumor development while potentially facilitating metastasis [29]. PTMs of PGK1-t255 enhances lactic acid production, thereby amplifying the proliferation rate of colon cancer cells and ultimately driving tumor progression [44]. Additionally, miR-548c-5p may exert its role as a suppressor of CRC by targeting PGK1 [93], while Islam Khan *et al.* [94] have also demonstrated that PGK1 holds promise as a biomarker for radiation therapy response in colon cancer tumors.

4.7 Other Cancers

The potential impact of PGK1 on various types of cancer is underscored by its significant role in glycolysis, and in addition to specific malignancies, PGK1 exerts influence on other forms of cancer.

Deletion of SMAD4 induces upregulation of PGK1 in pancreatic ductal adenocarcinoma (PDAC), which enhances glycolysis and invasiveness, and the unique localization pattern of PGK1 combined with PDAC progression can predict overall survival and disease-free survival [95]. Specific upregulation of PGK1 has been confirmed in renal clear cell carcinoma (KIRC), where increased expression in tumor tissue and serum indicates poor prognosis for patients [96]. In high-risk human papillomavirus (HPV) positive cervical epithelial squamous cell carcinoma (CESC) tissues, PGK1 expression is significantly higher compared to normal cervix tissues, resulting in shorter disease-specific survival (DSS) and progression-free survival (PFS) [97]. The overexpression of PGK1 is associated with the promotion of neuroblastoma bone marrow metastasis and exhibits

a negative correlation with patient prognosis [98]. A hypoxic environment promotes glycolysis by inducing PGK1 expression in oral squamous cell cancer cells (OSCs), promoting tumor spread [99]. YTHDF3 enhances the stability of PGK1 mRNA through an M6A-dependent mechanism while HCG18 enhances its expression; both promote osteosarcoma proliferation [17,100].

The Warburg effect is a distinctive trait observed in cancer and offers significant potential as a focus for both diagnostic and therapeutic approaches. Due to its crucial involvement in the development and advancement of multiple tumors, PGK1 emerges as an essential glycolytic kinase, making it a promising candidate for diverse anti-cancer interventions.

5. Potential Inhibitors of PGK1

Considering the significant impact of PGK1 on the advancement and growth of cancer, it emerges as a highly encouraging molecular target for therapeutic interventions against cancer. Consequently, there is immense potential in exploring PGK1 inhibitors to enhance the effectiveness of cancer treatments (Table 2, Ref. [7,29,99,101–104]).

In a study conducted by Hu *et al.* [30], it was observed that acetylation of PGK1 K323 plays a crucial role in regulating liver cancer. This modification enhances the activity of the enzyme and has an impact on the metabolism of cancer cells. Furthermore, bidirectional enzymes such as P300/cyclic adenosine monophosphate response element binding protein-associated factor (PCAF) and Sirtuin 7 were found to be involved in controlling K323 acetylation in liver cancer cells [30]. Therefore, these findings suggest that targeting P300, PCFA, and Sirtuin 7 could be a promising strategy for developing PGK1 inhibitors.

PGK1 has previously been documented to hinder its own function by disrupting the binding of lysine 220 (K220) to ADP, thereby exerting a negative regulatory impact on PGK1 activity. KAT9 and histone deacetylases 3 (HDAC3) have been identified as potential enzymes responsible for modifying the acetylation status of PGK1 through acetyltransferase and deacetylase activities respectively. The phosphorylation of HDAC3 at S424 enhances the interaction between HDAC3 and PGK1, resulting in the acetylation of K220 on PGK1 and subsequent inhibition of its enzymatic function [101].

Since 1988, bisphosphonates have been recognized as suppressors of PGK1 by diminishing its ability to bind with 1,3-BPG and reducing the enzyme's activity. This establishes them as one of the earliest artificially created competitors that inhibit PGK1 [102]. Moreover, CBR-470-1 (Fig. 4E) acted as a non-covalent modulator of Nrf2, a member of the Cap'n'collar (CNC) transcription factor family, thereby initiating the Keap1-Nrf2 cascade to protect SH-SY5Y neurons against MPP+ (1-methyl-4-phenylpyridine ion)-induced cytotoxicity primarily by inducing instability in PGK1 [103]. DC-PGKI (Fig. 4C, Ref. [104]), an ATP-

Table 2. Inhibitors for PGK1.

Inhibitors	Inhibitory mechanism	Advantages	Disadvantages	Type of cancer tested	Pharmaceutical licensing	References
P300, PCAF and Sirtuin7	Inhibit PGK1 K323 acetylation	Inhibit the activity of PGK1 and has an impact on the metabolism of cancer cells	Poor specificity	liver cancer	No	[29]
KAT9 and HDAC3	Inhibit PGK1 K220 acetylation	Inhibition of PGK1 binding to ADP	Poor specificity	No cancer research	No	[99]
Terazosin	Occupies the ADP/ATP binding site on PGK1	Relatively high specificity	Only inhibit PGK1 at high dosages; Need to be further modified and optimized	No cancer research	Yes	[7]
NG52	Inhibiting PGK1 activity while simultaneously enhancing PDH activity	Suppress glioma proliferation	The inhibitory effect on PGK1 is unsatisfactory	glioma	Yes	[104]
DC-PGKI	an inhibitor that competitively binds PGK1 with ATP	Stabiliz and inhibit the glycolytic activity and kinase function of PGK1 in laboratory settings as well as within living organisms	No cancer research	No cancer research	No	[102]
IlicicolinH	A non-ATP-competitive inhibitor of PGK1	Targets PGK1 in order to hinder the metabolic process of HCC cells, ultimately leading to the inhibition of cell proliferation and promotion of apoptosis	The structure needs to be reoptimized	HCC	Yes	[103]
CBR-470-1	Induce instability in PGK1 to achieve inhibition	Activate Keap1-Nrf2 cascade to protect SH-SY5Y neurons from MPP ⁺ -induced cytotoxicity	Uncertain inhibitory mechanism	Cervical cancer	Yes	[101]

HDAC3, histonedeacetylases 3; ADP, adenosine diphosphate; ATP, adenosine-triphosphate; HCC, hepatocellular carcinoma.

competitive inhibitor targeting PGK1, effectively stabilized PGK1 both *in vitro* and *in vivo*, resulting in the inhibition of glycolytic activity and suppression of PGK1 kinase function. In our investigation on inflammatory bowel disease (IBD), we demonstrated that DC-PGKI-mediated inhibition of PGK1 led to the accumulation and nuclear translocation of NRF2 (nuclear factor-erythroid 2-related factor 2, NFE2L2). Subsequently, NRF2 bound to adjacent regions of *IL-1 β* and *IL-6* genes, ultimately alleviating colitis symptoms in a mouse model induced by dextran sulfate sodium (DSS). These findings emphasize the regulatory role played by PGK1 in macrophages and suggest the potential therapeutic application of PGK1 inhibitors for treating IBD [104]. Furthermore, Regarding the mechanism of Terazosins (Fig. 4A) activation on P_{gk1}, the 1,3-diamino-6,7-dimethoxyisoquinoline structural motif exhibits a favorable fit within the ADP/ATP binding pocket. Consequently, Terazosins demonstrates approximately tenfold higher binding affinity towards PGK1 compared to its substrate ADP, thereby facilitating ATP release from PGK1. Simultaneously, heat shock protein 90 (Hsp90) is widely recognized as an inhibitor of caspase-mediated apoptosis through diverse mechanisms; however, it possesses minimal ATPase activity. Nevertheless, upon ATPase activation, Hsp90 enhances its interaction with client proteins. Studies have revealed that activated PGK1 can potentially augment Hsp90's ATPase activity and subsequently promote its association with Recombinant Apoptotic Peptidase Activating Factor 1 (Apaf-1) to impede apoptotic body formation or Bid cleavage. Alternatively, it may activate survival pathways by elevating nuclear factor kappa-B (NF- κ B) activity or sustaining Protein Kinase B α (Akt) kinase function. This discovery positions Terazosins as a novel protective agent approved for market use and unveils PGK1 as a promising target for potential development and repurposing into clinical drugs [8].

Through their investigation, Li *et al.* [105] successfully identified a new compound called Ilicicolin H (Fig. 4D) that acts as an inhibitor of PGK1. This compound effectively targets PGK1 in order to hinder the metabolic process of HCC cells, ultimately leading to the inhibition of cell proliferation and promotion of apoptosis [105]. Additionally, another inhibitor known as NG52 (Fig. 4B) was discovered through a comprehensive screening process for potential drugs. NG52 primarily works by inhibiting PGK1 activity while simultaneously enhancing PDH activity, thereby reversing the Warburg effect and effectively suppressing glioma proliferation [8,106].

The current studies on PGK1 small molecule inhibitors are limited in their progress due to the absence of potential lead compounds [30], suggesting that there is still significant room for advancement in the development of innovative PGK1 inhibitors for effective cancer therapy. Given the ubiquitous presence of PGK1 in normal cells and its pivotal role as an enzyme in cellular glucose metabolism

and other essential activities, caution should be exercised when employing PGK1 inhibitors due to potential adverse effects on normal cellular function. However, the precise nature of these side effects remains unclear and warrants further investigation.

6. Conclusions and Prospects

Metabolic reprogramming is a crucial hallmark of cancer biology [18–20]. Therefore, comprehending the metabolism-related genes in tumors holds immense significance. Despite inadequate oxygen intake, malignant tumors activate glycolysis, leading to the Warburg effect [21–23]. PGK1 serves as an indispensable enzyme for ATP production in the glycolysis pathway [26], catalyzing the conversion of 1,3-diphosphoglycerate into ADP and generating 3-phosphoglyceric acid and ATP. Ultimately, this process promotes cancer cell metabolism [13,27]. Notably, PTMs of PGK1 in tumor cells play a pivotal role in tumor metabolism and growth regulation. Moreover, in addition to abnormal expression in various tumor tissues to meet rapid tumor growth demands, PGK1 facilitates tumor migration and invasion while inducing autophagy and drug resistance in cancer cells [46]. The multifaceted involvement of PGK1 suggests its significant role across numerous types of tumors with broad research prospects within the field of oncology.

Therefore, there is an urgent need to develop therapeutic drugs that target PGK1 based on its functional characteristics. Studies have shown that the secretion of PGK1 into the extracellular space of cells provides a convenient method for liquid biopsy [72]. This also suggests that PGK1 has promising application prospects as a diagnostic and prognostic biomarker in liquid biopsy. However, the development of PGK1 inhibitors is challenging due to the lack of related lead compounds.

In conclusion, PGK1 holds significant value in diverse diagnostic, therapeutic, and prognostic applications. Consequently, the development of targeted therapeutic agents against PGK1 assumes equal importance.

Author Contributions

ALQ: conceptualization, methodology, software, investigation, data curation, visualization, resources, writing—original draft, writing—review and editing. XSW: methodology, software, investigation, data curation, visualization, resources, writing—original draft, writing—review and editing. QSZ: software, investigation, data curation, visualization, resources, writing—original draft, writing—review and editing. SQZ: visualization, resources, writing—original draft, writing—review and editing. LY: resources, writing—original draft, writing—review and editing. YS: conceptualization, methodology, software. YH: conceptualization, methodology. QL: supervision, visualization, writing—review, and editing. DXL: conceptualization, visualization, writing—review and editing.

ing. ZFG: formal analysis, supervision, writing—review, and editing. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to thank the staff at each participating institution for their support with data collection.

Funding

This research was supported by Guangdong Provincial Basic and Applied Basic Research Foundation (2022A151522004), and Shenzhen Nanshan District's new introduction discipline leader fund project (NSZD2023020).

Conflict of Interest

The authors declare no conflict of interest.

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