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Phosphoglycerate kinase 1 (PGK1) in cancer: a promising target for diagnosis and therapy

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Running title: PGK1: an overview in cancer.

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Abstract

Phosphoglycerate kinase 1 (PGK1) is the first critical enzyme to produce ATP in the glycolytic pathway. PGK1 is not only a metabolic enzyme but also a protein kinase, which mediates the tumor growth, migration and invasion through phosphorylation some important substrates. Moreover, PGK1 is associated with poor treatment and prognosis of cancers. This manuscript reviews the structure, functions, post-translational modifications (PTMs) of PGK1 and its relationship with tumors, which demonstrates that PGK1 has indispensable value in the tumor progression. The current review highlights the important role of PGK1 in anticancer treatments.

Key word

PGK1; Protein kinase; Glycolysis; Post-translational modifications; Cancer.

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1. Introduction

Hypoxia is a dominant feature of cancer. Under hypoxia condition, the metabolism of cancer cells is reprogrammed from oxidative phosphorylation to glycolysis [1, 2]. The glycolysis pathway changes from mitochondrial oxidative phosphorylation to aerobic phosphorylation [3]. With enough oxygen, glycolysis is also activated in malignant tumor cells, a metabolic change closely related to tumor cell metabolism which is known as the Warburg effect [4-6]. Unlike normal cells, most cancer cells produce lactic acid to generate energy, and maintain high glycolysis rates even in the presence of oxygen [7, 8]. More noticeably, the prominent characteristic of tumor cells is abnormal in energy metabolism. Phosphoglycerate kinase 1 (PGK1) is an essential enzyme to produce ATP in the glycolytic pathway [9]. PGK1 has many characteristics of oncogene, promoting the tumor cell proliferation, migration and invasion, and playing vital roles in the progression of various tumors. So PGK1 is an extremely important molecular target for tumor therapy, which has also become a research hotspot in recent years [10, 11]. However, up to now, the roles of PGK1 in its regulatory mechanisms are still unclear. This review will summarize the studies about PGK1 in cancer.

2. Overview of PGK1 structure and activity

PGK is a monomer, highly flexible glycolytic enzyme composed of two leaves, much like pliers, with a deep crack in the middle and the active site centered at the bottom of the crack. PGK is a bilobed enzyme with two functional domains, including the nucleotide binding domain (NBD) and the catalytic domain (CD). 3-phosphoglyceric acid binds to the N domain, and Mg-complex nucleotides bind to the C domain, increasing the structural stability of the whole PGK1 molecule [12]. Therefore, PGK enzyme will be comprehensive studied as a model system for dual-domain proteins, including PGKs of yeast, bacteria and mammals [13-15].

PGK exists in all organisms and contains 2-3 isozymes in most organisms. There are two subtypes of PGK1 and PGK2 in human genome, with similar structure and function, and more than 80% of similar amino acid sequences [16]. However, PGK1 and PGK2 have different distributions. Autosomal coded PGK2 is expressed during spermatogenesis [17], and the gene is located on chromosome 6 [18]. As an X-linked gene, PGK1 is constitutively expressed in all somatic cells and premeiotic cells [19, 20]. Fig. 1 depicts the amino acid sequence and tertiary

structure of PGK1. Mutations that produce clinical disease can be found in both C and N regions.

L-nucleoside analogues are the mirror images of natural nucleosides and they are increasingly seen as antiviral and anticancer drugs [21, 22]. In order to be activated, L-nucleoside needs to be phosphorylated into their respective triphosphate metabolites, which has recently been reported that PGK1 is involved in the final step of phosphorylation [23, 24]. The extensive specificity of PGK1 to its nucleotide substrates has been analyzed as a property that allows the enzyme to contribute to the effective phosphorylation of nucleotide-based anticancer drugs. These characteristics of the interaction between PGK1 and nucleotide can provide guidance for the development and design of anticancer drugs [25]. Moreover, PGK1 has certain tumor gene characteristics and is abnormally expressed in many human tumors, which is regulated by multiple mechanisms. Therefore, this manuscript mainly focuses on PGK1.

3. The functions of the PGK1

3.1 PGK1 is a key metabolic enzyme

Frequently, participating in glycolysis is the primary function of PGK1 [10]. In the second step of glycolysis pathway, PGK1 catalyzes the conversion of 1, 3-diphosphoglycerate to 3-phosphoglycerate and forms 1 molecule ATP, which is the first reaction to generate ATP in anaerobic glycolysis [26]. At the same time, the high-energy phosphate group of its substrate is transferred to ADP and generates ATP. This process of direct coupling between the phosphorylation of ADP or other nucleoside diphosphate as well as the dehydrogenation of the substrate is called substrate-level phosphorylation. It is of great significance to the continuous production of cellular energy under hypoxia conditions [27]. The growth of tumor cells requires certain energy and substances, and PGK1 could supply energy and material for tumor cells (Fig. 2).

3.2 PGK1 acts as a protein kinase

Protein kinases are important regulators of intracellular signal transduction pathways, mediating biological development and regulation, which are closely related to cell growth, division, differentiation, adhesion, movement and death [28]. For example, PGK1 plays a pivotal role in the occurrence and development of tumor not only as a metabolic enzyme, but

also as a protein kinase. Through pyruvate dehydrogenase kinase isoenzyme 1 (PDHK1) activation mediated by mitochondrial PGK1, tumor cells are able to inhibit mitochondrial pyruvate metabolism and promote Warburg effect. Mitochondrial PGK1 directly phosphorylates PDHK1 at Thr338. The subsequent PDHK1-mediated phosphorylation of pyruvate dehydrogenase E1α at Ser293 inhibits the pyruvate dehydrogenase complex (PDC) and the conversion of pyruvate and CoA to acetyl-CoA in the mitochondria [9]. This inhibitory effect reduces the use of pyruvate in mitochondria, increases the process of pyruvate producing lactic acid, and promotes the occurrence and development of tumors [29]. Moreover, PGK1 phosphorylates Beclin1 at Ser30, leading to conformational changes and activation of phosphatidylinositol III(PI)3-kinase VPS34, which produces phosphatidylinositol 3-phosphate (PI(3)P) that promotes indirect tumor development [30]. Meanwhile, Beclin1 phosphorylation at Ser30 was positively correlated with poor prognosis of the tumor [31, 32]. This is the most frequently altered pathways in cancer, and once being activated, it changes the metabolism of tumor cells [33]. In addition, PGK1 self-phosphorylates at Y324, which could be dephosphorylated by PTEN [34]. The improvement of protein kinase functions in tumor development may make PGK1 a promising target for the treatment of malignant tumors (Fig. 2).

3.3 PGK1 plays as a co-activator of transcription factors

PGK1 could affect the function of some transcription factors, such as β-catenin, a tumor-associated oncoprotein. PGK1 is the upstream regulator of β-catenin, which can affect tumor growth, proliferation, metastasis, invasion, angiogenesis and drug resistance [35-37]. PGK1 is transferred into the nucleus, and PGK1 is phosphorylated at S256 by casein kinase 2α (CK2α). Phosphorylated PGK1 binds to the kinase cell division cycle 7 (CDC7) and converts ADP to ATP. Thus, the inhibition of ADP on CDC7-ASK activity was removed, and DNA helicase recruitment to the starting point of replication, DNA replication, cell proliferation and tumor development were promoted. Even though the cytoplasmic activity of PGK1 is consistent with its activity as a glycolytic enzyme, nuclear translocation of PGK1 indicates its atypical activity as a co-activator of transcription factor in metastatic cells [38, 39]. So PGK1 plays as a co-activator of transcription factors (Fig. 3).

3.4 Post-translational modifications of PGK1 and its significance in tumor cells

Post-translational modifications (PTMs) promote protein functional diversity by regulating protein activity, stability, subcellular localization, and protein-protein interactions. PTM is an effective mechanism to expand gene coding and regulate cell physiological functions, and is associated with a variety of cellular pathways and diseases. Previous research has established that PTM of PGK1 plays an essential role in different biological processes and is closely related to multiple diseases, including tumors (Fig. 4).

3.4.1 Phosphorylation of PGK1

EGFR activation or K-Ras/B-Raf mutation and anoxia induced ERK activation leads to PGK1 Ser203 phosphorylation. PGK1 then phosphorylates and activates PDHK1 as a protein kinase in the mitochondria, leading to the phosphorylation and inactivation of the PDH complex, which can enhance glycolysis and promote cell proliferation and tumor development [9]. The phosphorylated PGK1 then binds to PIN1 and isomerizes cis-trans, exposing partial residues of PGK1. Recent evidence suggests that polarized M2 macrophages enhance the phosphorylation of PGK1 Thr243 mediated by 3-phosphoinositol-dependent kinase 1 (PDPK1) in tumor cells by secreting interleukin-6 (IL-6) [40]. They demonstrates a new mechanism that macrophages promote tumor growth, by regulating the metabolism of tumor cells, suggesting the potential of therapy to destroy the relationship between macrophages and tumor cells by inhibiting PGK1 phosphorylation.

3.4.2 Acetylation of PGK1

Several studies suggest that Acetyltransferase NAA10 is found to be related to PGK1 and acetylates PGK1 at K388, which promotes the occurrence and development of tumors by regulating autophagy [41]. Similarly, acetyltransferase ARD1 also interacts with PGK1 to acetylate PGK1 K388, and then acetylated PGK1 binds and phosphorylates Beclin1 at the S30 site, thus activating the necessary VPS34-Beclin1-ATG14L complex for autophagy formation [31]. KAT9 and HDAC3 are the potential acetyltransferases and deacetylases of PGK1. Furthermore, PGK1 can also acetylate at the K220 site, which inhibits the activity of PGK1 by blocking the binding of substrate AD. Acetylation of PGK1 at K220 can increase the production of ATP, 3-PG and NADPH in glycolysis [42]. Meanwhile, PCAF (P300/CBP-associated factor) is a synergistic transcriptional activator of p53 that promotes the acetylation of PGK1 at K323. Acetylation at the K323 site of PGK1 can enhance the activity of

PGK1 and affect the expression of PCAF and SIRT7 of liver cancer, thus promoting the occurrence and development of liver cancer [43]. In conclusion, targeting PGK1 may be an attractive cancer therapy.

3.4.3 O-glcnacylation of PGK1

O-linked N-acetylglucosamine (O-GlcNAc) is a common post-translational modification of proteins serine and threonine residues, which plays a crucial role in many biological regulatory processes, including transcription, translation, metabolic reprogramming and other biological processes [44, 45]. The abnormal expression of O-glcnacylation is closely related to many diseases and is elevated in various cancers. Recent studies have demonstrated that PGK1 can be modified reversibly and dynamically by O-GlcNAc at Thr255. O-glcnacylation can activate the activity of PGK1, thereby increasing the production of lactic acid. At the same time, PGK1 translocation to mitochondria was induced by the interaction between PGK1 and the transposition enzyme of the outer membrane complex (TOM20) [9]. In conclusion, o-glcnacylation of PGK1 at Thr255 can promote the proliferation and glycolysis of colon cancer cells, and affect TCA cycle and tumor development [46].

3.4.4 Ubiquitination of PGK1

Long-chain non-coding RNA (lncRNA) MetaLnc9 is involved in the occurrence and development of tumors. MetaLnc9 prevents PGK1 ubiquitination, leading to the activation of carcinogenic mTOR/AKT signaling pathway in non-small cell lung cancer [47]. Cell polarity is the key to tumor cell migration and invasion. Rab11-FIP2 interacts with PGK1, and promotes ubiquitination of PGK1 in cells, while the forced expression of PGK1 activates the AKT/mTOR signaling pathway, suggesting that the anticancer function of Rab11-FIP2 is mediated by PGK1-mediated inhibition [48-51]. However, there are no studies can confirm the ubiquitin modification site of PGK1, so exploring the ubiquitin modification site of PGK1 may be one of the strategies for PGK1 targeting tumor therapy.

3.5 Transcription factors regulate the expression of PGK1

The expression of PGK1 has been shown to be influenced by a series of signaling pathways of tumor microenvironment (hypoxia and nutrient status) and growth factors (Fig. 5). These signaling pathways regulate the expression of PGK1 through transcription factor networks. For instance, transcription factor MYC affects the metabolic process and cell growth

by affecting the expression of metabolism-related proteins. In clear cell renal carcinoma cells (ccRCC), MYC is recruited at the promoter region of PGK1, suggesting that the MYC pathway plays an important role in the regulation of PGK1 expression [52]. However, as a transcription factor, peroxidosomal proliferation-activated receptorγ (PPARγ) in breast cancer cells also negatively regulates the expression of PGK1, which leads to the decrease of ATP level and apoptosis and inhibits cell proliferation [53]. Similarly, HIF is a kind of oxygen conditions involved in cellular catabolism of transcription factors. HIF-1α and HIF-2α can act as transcription factors to affect the expression of PGK1 when hypoxia occurs in tumor cells of pheochromocytoma and paraganglioma. Inhibiting the transcriptional activity of HIF-1α will lead to the low expression of PGK1, reduce the glycolysis level of cells and inhibit the proliferation of tumor cells [54]. NFAT family consists of five transcription factors, namely, NFATc1, NFATc2, NFATc3, NFATc4 and NFAT5, which have pro-tumor effects in a variety of malignant tumors [55]. PGK1 is the direct target gene of NFAT5, and the NFAT5 knockout significantly reduces the expression of PGK1. NFAT5 promotes the proliferation of tumor cells and Warburg effect by regulating PGK1 [56].

Some tumor-associated migration factors can interact with PGK1. 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD5) is an indispensable enzyme associated with steroid hormone-dependent cancer metabolism. It can negatively regulate the expression of PGK1, and the deletion of 17β-HSD5 can make the high expression of PGK1 and promote cell proliferation [57]. The high level of CXCR4 enhances the expression of PGK1, increasing the secretion of vascular endothelial growth factor (VEGF) and interleukin-8(IL-8). Similarly, PGK1 can also up-regulate the expression of CXCR4, further promoting the expression of the stromal cell-derived factor CXCL12, which is involved in the CXCR4/CXCL12-PGK1 signaling pathway. These data indicate that PGK1 is a necessary regulator for tumor development and metastasis [38, 58].

When tumor cells in hypoxia microenvironment may accumulate hypoxia inducing factor (HIF) activating its target genes PGK1 and vascular endothelial growth factor (VEGF) expression level, it will promote the tumor cells to absorb glucose [59]. The expression of PGK1 is closely related to tumor cells. The silencing of PGK1 reduces the gene expression level and the survival rate of tumor cells. On the contrary, the high expression of PGK1 in

tumor cells will lead to the rapid growth of malignant tumors. If the mechanism of abnormal expression of tumor cells is further elucidated, more in vitro and in vivo results are needed to support it.

3.6 PGK1 acts as a disulfide reductase to inhibit cancer

PGK1 also have some new extracellular functions. For instance, PGK1 can act as a disulfide reductase to reduce disulfide bonds, induce proteolytic shearing and promote the change of fibrinolytic lysate to angiostatin [60-63]. Angiostatin limits tumor size by limiting angiogenesis and directly inhibiting osteoclast growth [64, 65].

3.7 PGK1 deficiency

Interestingly, in addition to the above functions, PGK1 has other functions, including mediating autophagy [41, 66-68], DNA replication and repair of mammalian cells [69, 70]. The abnormal expression of PGK1 is related to the occurrence of disease, and the mutation of PGK1 leads to the deficiency of PGK1. Lack of PGK1 has existed as a health problem for many years. PGK1 deficiency is a very rare genetic disease. About 40 cases have been reported since it was detected [71, 72]. PGK1 deficiency has aroused people's strong research interest. Although few cases have been reported, PGK1 deficiency is characterized by a global distribution [19]. PGK1 deficiency is associated with Parkinson's disease, hereditary nonglobular hemolytic anemia, neurological dysfunction, and myopathy [73, 74]. But so far, there is no specific treatment for PGK1 deficiency.

3.8 Clinical significance of PGK1 in many types of tumors

Under the condition of hypoxia, tumor cells can utilize ATP produced by PGK1, and PGK1 reversely influences energy metabolism to form hypoxia environment, there by promoting the proliferation ability of tumor cells. The abnormal expression of PGK1 can affect the migration and invasion of tumor cells [75]. PGK1 was also found to be a strong predictor of survival in both the primary tumor and the serum of patients [76], which indicates that the expression of PGK1 is significantly correlated with the prognosis prediction of tumor, affecting the survival of patients, and can be used as a prognostic marker of tumor [61, 77]. It has been reported that the high expression of PGK1 is negatively correlated with the prognosis through some data, which can provide targets for the research of new drugs [78]. Thus, the high expression of PGK1 leaves tumor cells in hypoxic state, which has become a vital factor in

predicting poor prognosis after radiotherapy [79, 80].

Metabolic reprogramming is an emerging and important symbol of tumor biology [81-83]. In many malignant tumor tissues, including breast cancer, colon cancer, glioma, lung cancer and liver cancer, the expression of PGK1 is significantly correlated with tumor proliferation, metastasis, occurrence, development and prognosis prediction [10, 36, 43, 53, 84, 85]. With the increasing incidence of cancer, the clinical diagnosis and treatment of cancer is urgent. Generally, PGK1 can be used as a diagnostic marker and a therapeutic target for tumors [86]. Therefore, we will focus on the role of PGK1 in the growth, proliferation, migration, invasion and prediction of poor prognosis of a variety of common malignant tumors, so as to provide a solution for the treatment of malignant tumors. However, its deeper molecular mechanisms need to be discovered in future studies.

3.8.1 Breast cancer

Breast cancer in situ is not fatal. However, breast cancer cells have lost the characteristics of normal cells, so the connections between the cells are loose, easy to fall off, metastasis, life-threatening [87, 88]. Deaths from breast cancer have fallen from their peak because of early findings and improved treatment [89-91]. But at present, breast cancer is still a common tumor disease threatening women physical and mental health. According to the American Cancer Society, breast cancer in situ accounts for a large proportion of new cancers worldwide [92]. The clinical significance of PGK1 in breast cancer is still unclear, so we focused on the progression and cancer characteristics of PGK1 in breast cancer.

PGK1 promotes the growth of breast cancer cells and the generation of lactic acid, which is the end product of glycolysis [9]. The downregulation of PGK1 can obviously inhibit the invasion of breast cancer cells and reverse the epithelial-mesenchymal transformation (EMT) process [93] and promote the Warburg effect [94]. The negative regulation of PGK1 in breast cancer cells can inhibit the proliferation of tumor cells [53]. PGK1 is a key target gene for the potential treatment of breast cancer. PGK1 was found to be highly expressed in metastatic and invasive ductal breast cancer cells [57]. The over expression of PGK1 was also significantly correlated with advanced tumor stage, indicating that PGK1 was closely related to the occurrence, development and metastasis of breast cancer [93]. The PGK1 and HIF-1α pathways stimulate the development and metastasis of breast cancer [95]. As far as we known,

breast cancer patients have a poor prognosis. The up-regulated expression of PGK1 is also related to poor prognosis of breast cancer patients [96]. Moreover, PGK1 is related to the resistance to taxol chemotherapy in breast cancer patients, and the higher the expression of PGK1, the shorter the survival period of patients, so PGK1 can predict the treatment effect of patients [27, 97]. In conclusion, PGK1 can be used as an important biomarker for targeted therapy of breast cancer.

3.8.2 Prostate cancer

Prostate cancer (PCa) has become the biggest killer of older men in the United States and Europe. Although the incidence of prostate cancer in China is not as high as that in Europe and America, it is on the rise in recent years. It is one of the most common malignancies threatening men, and almost all men die of PCa and its bone metastases [98, 99].

In PCa, the high expression of PGK1 inhibits the expression of related protein E-calcium sticky, reduces the adhesion between PCa cells and promotes the metastasis of tumor cells. An important link between PGK1 expression and CXCR4/CXCL12 has been reported in prostate cancer cells, where overexpression of PGK1 increases the cell metastasis rate [58]. PGK1 is highly expressed in PCa patients, and the high expression of PGK1 in stromal cells is released into the tumor environment to stimulate CXCR4/CXCL12 pathway and induce migration and invasion of PCa cells [79], it indicates that PGK1 can be used as a biomarker for PCa transfer. There was no significant correlation between PGK1 and patients age and tumor size, but it was significantly correlated with Gleason score, TNM stage, local infiltration, bone metastasis and serum PSA expression. PGK1 can be used as a prognostic marker for PCa patients [100]. Furthermore, CXCL12 signal plays an important role in PCa localization in bone marrow [58, 101-106]. The "seed and soil" hypothesis holds that tumor cells prefer to operate in organs that enrich the soil [107]. This suggests that PCa cells may be attracted by the factors released from the bone and thus migrate to the bone preferentially. [108]. PGK1 secreted by prostate cancer can regulate the formation of bone metastases [109]. In addition, PGK1 may promote osteogenesis without affecting vascular system [110-112]. The expression of PGK1 was significantly increased in the cells and tissues of prostate cancer, which further indicated that the high expression of PGK1 was related to the poor prognosis of prostate cancer [113]. As can be seen above, the high expression of PGK1 is significantly correlated with the poor prognosis

of PCa, which can be used as a prognostic marker of PCa. The poor prognosis of prostate cancer patients is gradually improving due to advances in systemic chemotherapy and radiotherapy.

3.8.3 Glioma

A glioma is a tumor of the spinal cord and brain. Glioma occurs in glial cells and helps nerve cells to work normally. Currently, glioma is mainly treated by surgical resection of the tumor, combined with chemotherapy, radiotherapy and targeted therapy, which have become the most important auxiliary treatments for glioma surgery. PGK1 was significantly upregulated in radiation-resistant astrocytomas [85, 114], which suggests that PGK1 may be involved in radiation-resistant phenotypes and as a potential biomarker for developing better treatments.

Down-regulating the expression of PGK1 protein has a radiotherapy sensitization effect on human glioma U251 cells [85, 115]. The main mechanism of radiotherapy sensitization is to improve tumor hypoxia so as to improve the radiosensitivity of glioma cells. The existing concurrent chemoradiotherapy drug temozolomide for glioma has been reported to have radiotherapy sensitization, which plays a crucial role in radiotherapy sensitization through the alkylation of guanine structure leading to DNA damage [116]. If the radiation sensitization of glioma can be carried out clinically in the future, the survival period of glioma patients can be effectively extended, and ideas for future research direction can be provided [117]. Hypoxia is known to play a central role in the pathobiology of gliomas. Hypoxia-driven physiologic changes include the glycolytic pathway regulation and bloodvessel formation [59], and also promote glioma cell migration and invasion [85, 118]. PGK1 T243 phosphorylation can be used as an indicator of gliomas prognosis biomarkers, and provides a new strategy for the treatment of gliomas [40]. Phosphorylation of PGK1-mediated Beclin1 at Ser30 is necessary to initiate autophagy, and phosphorylation of Beclin1 at Ser30 is positively correlated with poor prognosis of glioblastoma [31]. In addition, postoperative radiotherapy for glioma has become an important adjuvant therapy, which can help tumor patients get a good prognosis. In conclusion, PGK1 may provide new therapeutic methods for the treatment of glioma and provide new ideas. However, there is still a long way to go to use the level of PGK1 in glioma

as a potential indicator to predict clinical drug resistance. In order to confirm the role of PGK1 in glioma, more glioma cell lines should be included.

3.8.4 Liver cancer

Liver cancer generally refers to primary liver cancer, which refers to the cancer caused by liver cells or intrahepatic bile duct epithelial cells. Primary liver cancer is one of the most common malignant tumors in China, and ranks second in the mortality rate of malignant tumors [119, 120]. Each year there are nearly 600,000 deaths worldwide as a result of HCC, China accounts for over 50% of the world cases [121]. Scientists predict that the incidence of liver cancer will continue to rise in the next few decades, so it is urgent to develop drugs for the diagnosis, prognosis and treatment of liver cancer [121, 122]. The high expression of PGK1 is crucial to the proliferation and tumorigenesis of liver cancer cells, and may be a potential target for the treatment of liver cancer. PGK1 gene silencing in liver cancer cells decreases the survival rate and the proliferation of liver cancer cells [120]. PGK1 is overexpressed in liver cancer and can promote the proliferation of tumor cells, glycolysis and tumor development. The acetylation of the K323 site of PGK1 is related to the severity of liver cancer. The acetylation of PGK1 enhances the enzyme activity and promotes the occurrence and development of liver cancer, which can lay a foundation for the development of radiotherapy sensitizers targeted at the metabolic enzyme PGK1 [43]. But besides that, PGK1 level can be complementary with AFP, further improving the sensitivity and specificity of predicting liver cancer recurrence, suggesting that serum PGK1 level can be used as a new prognostic biomarker for predicting liver cancer recurrence after surgical treatment [123].

3.8.5 Lung cancer

Lung cancer is known as primary bronchial cancer, which is originated from the bronchial mucosa, or bronchial gland of a malignant tumor, clinical more common. There are two main clinical types of the disease: small cell lung cancer and non-small cell lung cancer (NSCLC) [124]. NSCLC is the most common disease in both men and women in many regions [125], and despite systematic treatment efforts worldwide [126, 127], poor prognosis persists [128]. In addition to surgery, various combination therapies, including chemotherapy and radiotherapy, have poor therapeutic effects on non-small cell lung cancer, and only a few patients can survive for 5 years [129]. At present, the incidence of lung cancer is very high,

causing people widespread attention. The high expression of PGK1 in lung cancer can inhibit the growth of tumor cells by down-regulating the expression of COX-2 [130]. In lung cancer, the high expression of PGK1 inhibits urokinase type plasminogen activator receptor (uPAR) and decreases the migration of tumor cells [84, 131]. PGK1 is a key positive regulator of angiogenesis switch, which is crucial for tumor proliferation and metastasis [58]. Moreover, the high expression of PGK1 in serum is correlated with the poor prognosis of lung cancer, which could predict the prognosis of early lung cancer [76].

3.8.6 Gastric cancer

Gastric cancer is a malignant tumor originated from gastric mucosa epithelium. It can not only cause damage to the digestive system, but also cause metastasis, which may affect the liver, kidney and respiratory function. Gastric cancer combined with peritoneal cancer is a common cause of cancer death worldwide [132, 133]. Although the death rate of gastric cancer is gradually decreasing in many countries, there is no effective treatment method at present, and the 5 years survival rate is still very low [134]. Overexpression of PGK1 in gastric cancer cells leads to a significant increase in the expression of the chemokine receptors CXCR4 and β-catenin, and blocking CXCR4 could inhibit cell invasion [135]. The overexpression of PGK1 increases the migration and invasion of gastric cancer cells [100]. PGK1 is considered as a prognostic molecular marker of gastric cancer or a potential therapeutic target to prevent the metastasis of gastric cancer cells to the peritoneum.

3.8.7 Other cancers

PGK1 not only affects the expression of malignant tumors, but also affects other cancers. For example, the increased expression of PGK1 in colon cancer is related to metastasis [36]. Pancreatic cancer is a highly malignant tumor of the digestive system, and survival rates are often very low in patients diagnosed. In SMAD4-negative pancreatic cancer, the nucleus PGK1 in the pancreatic cancer cells can participate in regulating gene transcription, thus enhancing the invasion and metastasis ability of pancreatic cancer cells. On the other hand, the cytoplasm PGK1 can serve as an important metabolic enzyme to promote the smooth intracellular sugar decomposition and provide energy to support the proliferation of pancreatic cancer cells [136]. In gallbladder cancer, the effect of PGK1 expression on the prognosis of patients is investigated, and the overexpression of PGK1 is significantly correlated with poor prognosis

[137]. In endometrial cancer, the expression of PGK1 is inversely proportional to the survival of patients, so PGK1 affects the prognosis prediction of patients, and the detection of PGK1 expression can more effectively evaluate the prognosis of patients with endometrial cancer [138]. Studies have shown that the down-regulation or up-regulation of PGK1 can respectively eliminate the increase or decrease of aerobic glycolysis caused by stable ectopic expression or ERG depletion [139].

The clinical significance of PGK1 in some cancers still requires further exploration. This needs a large number of *in vivo* and *in vitro* experiments to further study the important role of PGK1 in cancer, including the research progress, metastasis mechanism and drug resistance to radiotherapy (Table 1).

4. Conclusions and prospects

Taken together, in addition to maintaining cell metabolism as a glycolytic enzyme, PGK1 plays different roles in different cell intervals, thus showing the non-metabolic functions of PGK1 [140, 141]. In mitochondria, PGK1 can be used as a protein kinase to inhibit pyruvate metabolism and promote the Warburg effect. In the nucleus, PGK can increase the synthesis of DNA. In addition, PGK1 also plays an important role in tumor energy metabolism, and its abnormal expression in a variety of tumor tissues helps to meet the needs of rapid tumor growth. With the in-depth study of PGK1, the up-regulation or down-regulation mechanism of PGK1 not only plays a catalytic role, but also participates in the expression and regulation of various tumor proteins, affecting the development of tumor cells.

Biological process analysis showed that PGK1 is involved in post-translational modification and can interact with transcription factors, which is closely related to glycolysis, cell response to hypoxia, epithelial cell differentiation and gluconeogenesis. Abnormal expression of PGK1 can be detected not only in tumor tissues, but also in patients'peripheral blood and saliva. Therefore, PGK1 is a potential target of tumor therapy and a hot molecule in tumor therapy research. However, the role of PGK1 in different tumors is different, which may be related to the tissue specificity of PGK1 and the expression level in different tissues, which should be considered when developing drugs and tumor treatments for PGK1. In addition, how to develop therapeutic drugs targeting PGK1 according to the function of PGK1 is also an important issue. Therefore, PGK1 has a broad research prospect in cancer. Overall, I believe

that the development of new discoveries and insights may solve many of unknown problems.

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Figure Legends

Fig. 1. Amino acid sequence and structure of PGK1.

A. The Amino acid sequence of PGK1.

B. The structure of PGK1.

C. The function domain of PGK1.

Fig. 2. PGK1 have metabolic enzyme functions and protein kinase functions as well as co-activation.

Fig. 3. PGK1 plays as a co-activator of transcription factors.

Fig. 4. Post-translational modification of PGK1, including phosphorylation, acetylation, O-glcnacylation and ubiquitination.

Fig. 5. Various transcription factors regulate PGK1.

Table 1. Functions of PGK1 in several common malignant tumors.

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Table 1 Functions of PGK1 in several common malignant tumors

Cancer types	Function/clinical association		References
Breast cancer	Promote EMT process		93
	Promote the Warburg effect		94
	Inhibit the cell apoptosis		53
	Poor prognosis		27, 57
Prostate cancer	Induce migration and invasion		58
	Prognostic marker		100
	Regulate the formation of bone metastases		58, 79, 109
Glioma	Radiotherapy sensitization effect		85, 114, 115
	Bloodvessel formation		85
	Promote the cell migration and invasion		85, 118
	Poor prognosis		31, 40
Liver cancer	Promote the proliferation		120
	Radiotherapy sensitization effect		43
	Poor prognosis		123
Lung cancer	Affect the cell migration and proliferation		84, 130, 131
	Poor prognosis		76, 128, 129
Gastric cancer	Affect the cell migration and proliferation		100, 135
	Poor prognosis		134

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The authors have declared no conflict of interest

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