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Progress in PGK1 in Prostate Cancer

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Abstract: Phosphoglycerol kinase 1 (PGK1) is the first key metabolic enzyme that produces ATP during glycolysis and is involved in the glycolytic pathway of prostate cancer. PGK 1 can not only act as a metabolic enzyme to affect tumor growth, but also affect the gene expression, energy metabolism, molecular regulation and other processes of tumor cells through its non-metabolic enzyme function, and then mediate the growth, migration and invasion of tumors, and aggravate the biological characteristics of malignant cancer cells. In this review, we reviewed the structure and function of PGK1 and its relationship with prostate cancer to clarify the important role of PGK1 in the progression of advanced adenoma and provide a theoretical basis for targeting PGK1 for drug development.

Keywords: PGK1; Prostate Cancer; Phosphoglycerol Kinase 1; Glycolysis.

1. Introduction

Prostate cancer, a malignant tumor that poses a significant threat to men's health worldwide, has a complex pathogenesis involving multiple biological processes [1]. Metabolic reprogramming is a key characteristic in the development of prostate cancer, where changes in metabolic pathways provide a material basis for the disease and may affect the biological behavior of the tumor [2]. Phosphoglycerate kinase 1 (PGK1), as a key enzyme in the glycolytic pathway, plays an important role in the energy metabolism of tumor cells, especially in prostate cancer, where the expression level of PGK1 is closely related to the malignancy of the tumor and the prognosis of the patient [3]. The metabolic reprogramming of prostate cancer includes not only changes in the glycolytic pathway but also the reprogramming of lipid metabolism [4]. Studies have shown that prostate cancer cells rely more on the fatty acid oxidation pathway for metabolic reprogramming to obtain energy substances [5]. In addition, the metabolic characteristics of prostate cancer stem cells are significantly different from those of ordinary prostate cancer cells, such as the enhanced activity of the urea cycle in prostate cancer stem cells, and proline promotes tumor stemness through the JAK2-STAT3 signaling pathway [6]. The role of PGK1 in prostate cancer is not limited to its function in glycolysis; it may also affect the gene expression and molecular regulation of tumor cells through its non-metabolic functions, thereby mediating tumor growth, migration, and invasion [7]. Abnormal expression of PGK1 is closely related to the occurrence and development of various tumors, including its overexpression in prostate cancer, which may be related to its role in promoting the proliferation, colony formation, migration, and invasion of tumor cells. In summary, the metabolic reprogramming of prostate cancer, especially the role of PGK1, provides a new perspective and potential targets for the diagnosis and treatment of prostate cancer. Future research needs to further explore the specific mechanisms of PGK1 in prostate cancer and how to effectively use this knowledge to develop new treatment methods.

2. Main Body

2.1. Structure of PGK1

Phosphoglycerate kinase (PGK) is a monomer glycolytic enzyme with a typical double-domain hinged structure, conserved in sequence across all organisms throughout the evolutionary process [8]. PGK consists of two identical α-helical structural domains. The N-terminal domain binds to 3-phosphoglycerate (3-PG) or 1,3-bisphosphoglycerate (1,3-BPG), while the C-terminal domain binds to MgADP or MgATP. The binding of 3-phosphoglycerate and Mg-nucleotide complex to the N-terminal and C-terminal domains, respectively, enhances the overall structural stability of the molecule [9]. Mutations in the N-terminal or C-terminal domain can lead to clinical diseases [10-11]. PGK has two isoforms, PGK1 and PGK2, with different expression patterns. PGK2, encoded by a gene on chromosome 6, is expressed only during spermatogenesis, while PGK1, encoded by an X-linked gene, is ubiquitously expressed in all cells, providing the potential for PGK1 to serve as a target for cancer therapy [12-13].

2.2. Function of PGK1

2.2.1. Metabolic Enzyme Function of PGK1

The occurrence and development of prostate cancer rely on the supply of materials and energy, with enhanced glycolytic activity being one of its important metabolic characteristics [14]. Under aerobic conditions, prostate cancer cells preferentially undergo energy metabolism through the glycolytic pathway that produces lactate, a phenomenon known as the Warburg effect [15]. As one of the key metabolic enzymes in the glycolytic process, the role of PGK1 in prostate cancer is particularly significant. It catalyzes the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate in the second step of the glycolytic pathway, forming one molecule of ATP in the process, which is the first reaction in anaerobic glycolysis to produce ATP [15]. The transfer of the high-energy phosphate group from PGK1's substrate to ADP to generate

ATP is of great importance for the continuous production of cellular energy under hypoxic conditions [16]. Therefore, PGK1 may become an attractive therapeutic target in the treatment of prostate cancer. The mechanisms of PGK1 as a metabolic enzyme in regulating prostate cancer cells can be considered for the following intervention pathways: 1) Blocking the signal transduction pathways of metabolic enzyme nuclear translocation; 2) Designing specific inhibitors targeting nuclear metabolic enzymes; 3) Blocking the binding of nuclear metabolic enzymes with transcriptional complexes; 4) Specifically inhibiting the protein kinase activity of metabolic enzymes without affecting their metabolic enzyme activity. These intervention strategies provide a new perspective for the interventional treatment of prostate cancer.

2.2.2. PGK1 as a Protein Kinase

Protein kinases are essential regulators of intracellular signal transduction pathways, mediating biological development and regulation, and are closely associated with cell growth, division, differentiation, adhesion, movement, and death [17]. PGK1, acting as a protein kinase, phosphorylates its substrates Beclin1 and pyruvate dehydrogenase kinase 1 (PDHK1), affecting the processes of tumorigenesis [18]. Li X et al. found that PGK1 can translocate to the mitochondria under hypoxic stress, epidermal growth factor receptor (EGFR) activation, or expression of oncogenic K-Ras G12V or B-Raf V600E mutations [19]. Once in the mitochondria, PGK1 phosphorylates PDHK1 at the Thr338 site, inhibiting mitochondrial oxidative phosphorylation, increasing extracellular acidification and lactate production, thereby promoting tumorigenesis [20]. Qian X et al. discovered that loss of PTEN function often occurs in tumor cells, leading to increased autophosphorylation of PGK1, enhanced glycolysis, and ATP production, promoting cell proliferation and tumorigenesis [21]. Moreover, the rapid growth of tumors can cause existing blood vessels to be unable to grow and induce ischemia within the tumor, leading to metabolic stress and inducing autophagy to maintain cellular homeostasis [22]. Under hypoxic or glutamine-deprived conditions, mTOP-mediated phosphorylation of the acetyltransferase ARD1 at the S228 site leads to ARD1-dependent acetylation of PGK1 at the K388 site. The acetylated PGK1 then phosphorylates Beclin1 at the Ser30 site, regulating intracellular transport and the formation of autophagosomes, promoting the occurrence and development of tumors [23]. The abnormal activity of PGK1 in prostate cancer may promote the occurrence and development of tumors through various mechanisms [24]. Under hypoxic, EGFR-activated, or specific oncogenic gene mutation conditions, PGK1 can translocate to the mitochondria and inhibit mitochondrial oxidative phosphorylation by phosphorylating the Thr338 site of PDHK1, thus increasing extracellular acidification and lactate production, and promoting tumorigenesis. Additionally, the common loss of PTEN function in tumor cells leads to increased autophosphorylation of PGK1, thereby enhancing glycolysis and ATP production, and promoting the proliferation of tumor cells. Under hypoxic or glutamine-deprived conditions, the interplay between the acetylation of PGK1 and the phosphorylation of Beclin1 regulates intracellular transport and the formation of autophagosomes, further promoting tumor development. These findings suggest that the protein kinase activity of PGK1 plays a key role in the metabolic reprogramming and adaptiveness of tumor cells in prostate cancer and may become a promising target for prostate cancer therapy. Therapeutic strategies targeting PGK1, such as the use of small molecule inhibitors to intervene in the activity of PGK1, may help inhibit the proliferation and invasion of tumor cells, providing new treatment options for prostate cancer patients.

2.3. PGK1 as a Coactivator of Transcription Factors

During the development of prostate cancer, β-catenin, as a tumor-associated protein, is involved in the regulation of cell proliferation, invasion, metastasis, angiogenesis, and drug resistance [25]. PGK1, acting as an upstream regulator of β-catenin, can influence the occurrence and development of tumors by affecting the function of β-catenin [26]. In addition, the early growth response family member EGR1 is also closely related to the activity of PGK1 [27]. Li X et al. found that PGK1 is phosphorylated at the S256 site by EGFR- and ERK-activated casein kinase 2a (CK2a), which then interacts with the kinase cell division cycle 7 (CDC7), promoting the conversion of ADP to ATP [28]. In tumor cells, the expression of PGK1 S256A can block the activation of EGFR, thereby affecting the activity of CDC7-ASK, the assembly of DNA helicase, DNA replication, cell proliferation, and the occurrence and development of tumors. At the same time, PGK1 can also act as a co-chaperone of Hsp90, participating in the folding, maturation, and stability of various proteins, thus being involved in the occurrence and development of tumors [29]. It is worth noting that the nuclear translocation of PGK1 reveals its atypical activity as a coactivator of transcription factors in metastatic cells, indicating that PGK1 may have a more complex regulatory role in prostate cancer.

2.4. PGK1 as a Key Downstream Target of the Chemokine Axis

The expression of PGK1 in prostate cancer is typically influenced by the tumor microenvironment and signaling pathways such as growth factors. Intratumoral hypoxia plays a significant role in the recurrence, spread, and resistance to radiochemotherapy of prostate cancer. Intratumoral hypoxia can induce the activation of Hypoxia-inducible factors (HIFs) [30]. In pheochromocytomas and paragangliomas, tumor cells under hypoxic conditions activate the target genes HIF-1α and HIF-2α, which act as transcription factors to promote the expression of PGK1, enhance glycolytic levels, and thus drive the proliferation of tumor cells [31]. Additionally, the transcription factor MYC also affects the expression of metabolic-related proteins through PGK1, thereby influencing cell growth [32]. Tang SW et al. found in clear cell renal cell carcinoma that activated MYC could induce the upregulation of PGK1 expression, promoting the proliferation of tumor cells [33]. In breast cancer, the peroxisome proliferator-activated receptor γ (PPARγ) as a transcription factor is also involved in the regulation of PGK1 expression [34]. Moeller BJ et al. showed that a reduction in reactive oxygen species leads to decreased sensitivity of the hypoxic part of tumor cells to treatment, and HIF activated under hypoxic conditions can activate downstream target genes PGK1 and vascular endothelial growth factor (VEGF), as well as the release of other

angiogenic cytokines, promoting tumor growth and enhancing the resistance of tumor cells to radiotherapy [35]. Type 5 17β-hydroxysteroid dehydrogenase (17β-HSD5) is an important enzyme related to sex steroid metabolism in hormone-dependent cancers [36]. Knockout of 17β-HSD5 can increase the expression of PGK1, and the silencing of PGK1 reduces the gene expression level and survival rate of tumor cells [37]. Stromal cell-derived factor (CXCL12) and its receptor chemokine (CXCR4) are related to the occurrence and development of tumors, and the interaction between PGK1 and CXCR4/CXCL12 positively regulates and participates in the CXCR4/CXCL12-PGK1 signaling pathway, promoting tumor metastasis [38]. Studies have shown that PGK1 is significantly correlated with the Gleason score, TNM staging, local infiltration, bone metastasis, and serum PSA expression in prostate cancer, and PGK1 can serve as a prognostic marker for prostate cancer patients [39]. As a key downstream target of the chemokine axis, PGK1 is also an important regulator of the tumor "angiogenesis switch" [40].

2.5. Post-translational Modifications of PGK

Post-translational modifications (PTMs) are a series of chemical modifications that proteins undergo after RNA translation, which have significant effects on the structure and function of proteins [41]. In prostate cancer, PTMs such as phosphorylation, glycosylation, ubiquitination, methylation, acetylation, and proteolysis are involved in regulating various biological processes of tumor cells and are closely related to the occurrence, development, and metastasis of tumors [42]. PTMs of PGK1, especially phosphorylation, can affect its enzymatic activity and interactions with other proteins, thereby playing an important role in the metabolic reprogramming, proliferation, migration, and invasion of tumor cells [43]. Studies have shown that the abnormal expression of PGK1 is closely related to the malignant phenotype of prostate cancer, and its overexpression may promote the glycolytic process of tumor cells, providing energy support for the rapid proliferation of tumor cells [44]. In addition, the non-metabolic enzyme functions of PGK1, such as its role as a protein kinase, may also affect the gene expression and molecular regulation of tumor cells through PTMs, thus playing a key role in the development of prostate cancer. Therefore, in-depth research on the PTMs of PGK1 in prostate cancer and their regulatory mechanisms will help to reveal the molecular mechanisms of prostate cancer and provide a theoretical basis for the development of new therapeutic strategies.

2.5.1. Phosphorylation of PGK1

During the development of prostate cancer, the activation of EGFR, mutations in K-Ras/B-Raf, or hypoxic conditions can all induce the activation of ERK, leading to the phosphorylation of PGK1 at Ser203. This phosphorylation event activates PDHK1, which in turn promotes the phosphorylation and inactivation of the PDH complex, inhibiting the utilization of pyruvate in the mitochondria [45]. This series of changes ultimately leads to an enhancement of the glycolytic process, providing favorable conditions for the occurrence and development of tumors. Furthermore, in malignant gliomas, macrophages enhance the phosphorylation of PGK1 at Thr243 by 3-phosphoinositide-dependent protein kinase-1 (PDPK1) in tumor cells through the production of interleukin-6 (IL-6). This phosphorylation alters the substrate affinity of PGK1, thereby promoting the glycolytic reaction catalyzed by PGK1. Knocking out the PGK1 gene can eliminate the macrophage's promotion of tumor cell proliferation. This finding reveals a new mechanism by which macrophages regulate tumor cells through the phosphorylation of PGK1. The activation of EGFR or mutations in K-Ras/B-Raf, as well as ERK activation induced by hypoxia, may lead to the phosphorylation of PGK1 at Ser203. In addition, the phosphorylation status of PGK1 may have potential clinical significance in the prognostic assessment of prostate cancer.

2.5.2. Acetylation of PGK1

During the development of prostate cancer, glutamine deprivation and hypoxic environments can inhibit the phosphorylation of the acetyltransferase ARD1 at the S228 site mediated by mTER. This inhibition leads to the binding of ARD1 with PGK1 and promotes the acetylation of PGK1 at the K388 site. The acetylated PGK1 further binds with Beclin1 at the S30 site and promotes its phosphorylation, activating the Beclin1-VPS34-ATG14L complex, thereby initiating the autophagy process, which affects tumor growth. Acetylation of PGK1 at lysine 220 (K220) inhibits the activity of PGK1 by disrupting the binding with its substrate ADP, thereby affecting tumor growth. Moreover, in liver cancer patients, P300/CBP-associated factor (PCAF) and Sirtuin7 (SIRT7) are enzymes that regulate the bidirectional acetylation of PGK1 at the K323 site. The acetylation at the K323 site can enhance the metabolic enzyme activity of PGK1, improving the enzymatic activity of PGK1 and the metabolic level of cancer cells, providing a theoretical basis for the development of radiation sensitizers targeting the metabolic enzyme PGK1.

2.5.3. Ubiquitination of PGK1

The long non-coding RNA (IncRNA) MetaLnc9 interacts with PGK1 and prevents the ubiquitination of PGK1 in prostate cancer cells, leading to the activation of the oncogenic AKT/mTOR signaling pathway [46]. In addition, the interaction between Rab11-FIP2 and PGK1 enhances the ubiquitination of PGK1 within the cell, reducing the phosphorylation level of AKT/mTOR, indicating that the tumor-suppressing function of Rab11-FIP2 is mediated by the inhibition of PGK1 [47]. Cai Q et al. found in gallbladder cancer that GBCDRlnc1 inhibits the ubiquitination of PGK1, leading to an increase in the expression of the autophagy initiator ATG5-ATG12 complex, thereby enhancing autophagy and increasing the drug resistance of tumor cells [48]. Chu Z et al. found in breast cancer patients that IncRNA LINC00926 enhances the ubiquitination of PGK1 mediated by the E3 ligase STUB1, downregulating the expression of PGK1 [49]. However, no studies have yet determined the modification sites of ubiquitination. Therefore, exploring the ubiquitination modification sites of PGK1 may become one of the new strategies for targeted therapy of prostate cancer.

2.5.4. Glycosylation of PGK1

O-Linked beta-N-acetylglucosamine (O-GlcNAc) modification is a post-translational modification that occurs on the serine and threonine residues of proteins and

has significant effects on biological processes such as transcription, translation, metabolic reprogramming, and immune regulation [50]. In prostate cancer, research by Nie H et al. has found that PGK1 can be modified by O-GlcNAcylation at the T255 site, and this modification can increase the activity of PGK1 and enhance lactate production. Concurrently, O-GlcNAcylation induces the translocation of PGK1 to the mitochondria, leading to the inactivation of the pyruvate dehydrogenase complex (PDH complex), reducing the level of mitochondrial oxidative phosphorylation, enhancing the glycolytic process, and weakening the tricarboxylic acid (TCA) cycle, thereby promoting tumor growth [51]. This provides a theoretical basis for future targeted therapy of prostate cancer.

2.5.5. Succinylation of PGK1

In the study of prostate cancer, the overexpression of SIRT5 is believed to potentially regulate the glycolytic activity of PGK1 through the modulation of succinylation modification [52]. Specifically, research in renal cancer has found that SIRT5, as a potential tumor suppressor gene, regulates the glycolytic activity of PGK1 by affecting its succinylation modification levels [53]. Under conditions of SIRT5 overexpression, the succinylation modification level of PGK1 at lysine residues is reduced, which may further affect the proliferation and migration of tumors. However, the specific sites of SIRT5 action on PGK1 require further research to clarify. Although this research was conducted in renal cancer cells, its findings may have reference value for understanding the interaction between SIRT5 and PGK1 in prostate cancer.

2.6. Inhibition of Cadherin Expression by PGK1 Affects Tumor Occurrence and Development

E-Cadherin is an important epithelial cell adhesion molecule that plays a key role in inhibiting tumor invasion and metastasis [54]. In prostate cancer, the expression level of E-cadherin is closely related to the malignancy and progression of the tumor [55]. Studies have shown that high expression of PGK1 in prostate cancer cells suppresses the expression of E-cadherin, leading to reduced adhesion between tumor cells and promoting cell migration and invasion. Furthermore, the cytoplasmic localization of PGK1 mainly participates in the glycolytic process and promotes cell proliferation, while the nuclear localization of PGK1 may suppress the expression of E-cadherin through transcriptional regulation, further promoting the metastasis of prostate cancer [56]. These findings suggest that the high expression of PGK1 is significantly correlated with poor prognosis in prostate cancer and may become a prognostic marker for prostate cancer.

2.7. PGK1 Can Promote the Formation of the Tumor Microenvironment

The microenvironment of prostate cancer plays a crucial role in the occurrence and development of the tumor. Studies have shown that in prostate cancer, the expression of PGK1 is closely related to tumor immune infiltration, and it is positively correlated with tumor-infiltrating immune cells such as CD8+ T cells and activated NK cells [57]. The activity of PGK1 helps to maintain the interaction between cancer and the tumor microenvironment, which may promote the formation of an inflammatory phenotype in prostate cancer [58]. Research in prostate cancer has found that PGK1 plays a central role in the induction of the CAF (cancer-associated fibroblasts) phenotype in fibroblasts to the tumor microenvironment [59]. Moreover, overexpression of PGK1 in mouse lung cancer cells not only promotes the secretion of IFN-γ by T lymphocytes, enhancing the anti-tumor cellular immune response, but also inhibits the production of IL-10, reducing tumor-mediated immune suppression, thereby inhibiting tumor growth [60]. Shichijo S et al. also observed in HLAA2+ positive colon cancer that PGK1 could stimulate the production of IFN-γ, improve the killing effect of T lymphocytes, and thereby inhibit tumor growth [61]. These research results indicate that PGK1 may affect the immune response and prognosis of prostate cancer by regulating the activity of immune cells in the tumor microenvironment. Therefore, a deeper understanding of the mechanism of PGK1 in the immune microenvironment of prostate cancer may help to develop new immunotherapy strategies and improve the treatment outcomes for patients with prostate cancer.

3. Discussion

In recent years, there has been an in-depth understanding of the crosstalk between metabolic reprogramming and epigenetic modifications in prostate cancer and their mechanisms of action in tumor development. PGK1, as a multifunctional metabolic enzyme, plays a role in prostate cancer that goes beyond its key role in the glycolytic pathway to include non-metabolic functions, such as protein kinase activity, interaction with transcription factors, and effects on cellular signaling pathways. The abnormal expression of PGK1 plays a crucial role in the occurrence and development of prostate cancer, with its high expression level being closely related to the malignant phenotype of the tumor, potentially by promoting the glycolytic process of tumor cells, providing energy support for the rapid proliferation and metastasis of tumor cells. In addition, the changes in the expression level of PGK1 in prostate cancer tissue can not only serve as an important biomarker for tumor diagnosis and prognosis assessment but also have a significant impact on the metabolism and immune escape of tumor cells due to its dynamic changes in the tumor microenvironment, such as its expression in tumor-associated macrophages. Therefore, PGK1 is a potential target in the treatment of prostate cancer, and the development and research of drugs targeting PGK1 may provide new treatment strategies for patients with prostate cancer. At the same time, the abnormal expression of PGK1 may also be detected from the patient's peripheral blood and saliva, providing new possibilities for non-invasive tumor detection and prognosis assessment. In summary, PGK1 shows broad application prospects in the research and treatment of prostate cancer and is worth further experimental research and clinical exploration.

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