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Emerging roles of cytosolic phosphoenolpyruvate kinase 1 (PCK1) in cancer

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A B S T R A C T

Although it was traditionally believed that gluconeogenesis enzymes were absent from cancers that did not originate in gluconeogenic organs, numerous investigations have shown that they are functionally expressed in a variety of tumors as mediators of shortened forms of Gluconeogenesis. One of the isomers of PEPCK, the first-rate limiting enzyme in gluconeogenesis, is PCK 1, which catalyzes the conversion of oxaloacetate (OAA) and GTP into PEP, CO2, and GDP. It is also known as PEPCK-C or PCK1, and it is cytosolic. Despite being paradoxical, it has been demonstrated that, in addition to its enzymatic role in normal metabolism, this enzyme also plays a role in tumors that arise in gluconeogenic and non-gluconeogenic organs. According to newly available research, it has metabolic and non-metabolic roles in tumor progression and development. Thus, this review will give insight into *PCK1* relationship, function, and mechanism in or with different types of cancer using contemporary findings.

1. Introduction

1.1. Background

Cancer cells use glycolysis to get energy and metabolic intermediates for the synthesis of biomolecules, including lipids, proteins, and nucleic acids, whether oxygen is present or not. The Warburg effect is what is meant by this [1,2]. Cancer cells restrict other metabolic pathways, including gluconeogenesis and gluconeogenic enzymes. Yet, it has recently been found that some metabolic enzymes and metabolites in cancer cells have extra activities that are different from their original involvement in metabolic reactions [3]. For instance, it has been shown that many malignancies affect gluconeogenic enzymes, particularly phosphoenolpyruvate carboxylase (PEPCK) [4,5].

A gluconeogenic enzyme called phosphoenolpyruvate carboxy kinase (PEPCK) exists as cytoplasmic (*PCK 1*) and mitochondrial (*PCK 2*) isoforms [6]. It is a rate-limiting enzyme that uses the addition of phosphate to pyruvate and the simultaneous cleavage of CO2 from oxaloacetate to catalyze the conversion of oxaloacetate (OAA) and GTP into phosphoenolpyruvate (PEP) and CO2 [7]. It is now becoming clear that some cancer cells use it as a novel regulator for a specific metabolic pathway for biosynthesis in a nutrient-poor environment [8].

In colon-derived cancers, *PCK1* or PEPCK-C, was shown to be significantly expressed. By raising cellular glutamine levels, *PCK1* upregulates TCA activity. On the other hand, lung cancer, non-small cell lung cancer (NSCLC), kidney, thyroid, bladder, and breast malignancies all have high levels of *PCK-2* expression. Hence, it was suggested that increased cell proliferation might have been caused by the overexpression of these enzymes [9,10].

Quite apart from the data, it is still unclear how *PCK1* functions in cells other than non-tumorigenic cells. Consequently, using strong pieces of evidence, this review will shed light on the relationship, function, and mechanism of *PCK1* in or with a variety of cancers.

2. Role of PEPCK in gluconeogenesis

2.1. Gluconeogenesis

For mammals, glucose is necessary for the red blood cells, renal medulla, testes, skeletal muscles, heart, lens, and cornea. Thus, gluconeogenesis, a process that maintains the glucose level, is required for these organs to function normally [11].

The process of producing glucose from non-carbohydrate precursors such as glycerol, lactate, pyruvate, and glucogenic amino acids is known as gluconeogenesis. When there is a depletion of glycogen stores, it helps to maintain normal blood glucose levels after extended fasting or intense activity [12]. Apart from seven enzyme-catalyzed events that correspond to the reverse phases of glycolysis, the complete process has consisted of 11 enzyme-mediated reactions that were located in the mitochondria, endoplasmic reticulum (ER), and cytoplasm [13,14]. These specific reactions, which are catalyzed by the enzymes pyruvate carboxylase (PC) and PEPCK, fructose-1, 6-bisphosphatase (FBPase),

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and glucose-6-phosphatase (G6Pase), are necessary to circumvent irreversible steps in glycolysis [14,15].

2.1.1. Gluconeogenesis and Diseases

Several disorders are associated with alterations in gluconeogenic enzymes. Deficiency of pyruvate carboxylase results in Hypoglycemia, hepatomegaly, citrullinemia, lactic acidosis, etc. [16,17].

Deficiency of glucose-6-phosphatase (the enzyme that catalyzes the final step of gluconeogenesis as well as glycogenolysis) results in glycogen storage disease Ia (GSDIa), also called von Gierke's disease. It is characterized by fasting hypoglycemia, hyperuricemia, hepatomegaly, hyperlipidemia, growth retardation, etc. [18–20]. It is also associated with disrupted autophagy, enhanced hexose-monophosphate, and liver glycolysis. This will in turn maintain a carcinogenic environment due to upregulated expression of c-Myc, elevated glucose-6-phosphate dehydrogenase activity, an increased level of NADPH, and decreased glutathione [20].

Additionally, the production of glucose from all gluconeogenic substrates is impaired in FBPASE deficiency. This results in hypoglycemia at the time of prolonged fasting, together with the accumulation of gluconeogenic substrate [21]. Similarly, a deficiency of PEPCK was identified in the 1970s. Little evidence indicated that PEPCK deficiency is characterized by recurrent hypoglycemia along with neuroglycopenic symptoms such as lethargy, unconsciousness, or convulsions, frequent multisystem damage including hepatomegaly, renal tubular dysfunction, brain damage with developmental delay and failure to thrive, and hepatic dysfunction with cardiomyopathy [22,23].

Regarding cancer, those enzymes are downregulated and/or upregulated depending on the type of cancer. They promote cancer progression, growth, and metastasis by enhancing anaplerotic reactions, especially by modulating cell signals [24,25]. G6PC, for instance, is upregulated in glioblastoma [26]. By blocking the G1/S phase transition of the hepatoma cell cycle and the expression of associated cyclins, it prevents the proliferation of hepatoma cells. G6PC can also prevent the migration of hepatoma cells [27]. On the contrary, by stimulating the PI3K/AKT/mTOR signaling pathway, G6Pasecan hasten cervical cancer proliferation and metastasis [28].

On the other hand, decreased levels of Fructose bisphosphates (FBPase) were reported in cervical, gastric, and liver cancers, lung adenocarcinoma (LUAD), and liver hepatocellular carcinoma (LIHC) [29–32]. By causing pyruvate kinase M_2 (PKM_2) ubiquitination, FBP2 impeded aerobic glycolysis, which in turn prevented the proliferation of cervical cancer cells [33]. Additionally, it may prevent oral squamous cell carcinoma (OSCC) cells from proliferating, migrating, and undergoing glycolysis [34]. Emerging studies have also revealed the role of other gluconeogenetic enzymes in cancer, particularly PEPCK.

2.1.2. PEPCK

Utter and Kurahashi discovered phosphoenolpyruvate carboxykinase (PEPCK) (GTP) (EC 4.1.1.32) in the 1950s. It is the first step's rate-limiting enzyme and is highly conserved across species [35,36]. It is a crucial enzyme in the synthesis of glycerol in white adipose tissue and the small intestine, as well as glucose in the liver and kidney [37,38].

PEPCK has two isoforms: the cytosolic, PEPCK-C and mitochondrial, PEPCK-M. PEPCK-M also known as PEPCK2 or *PCK2*, was isolated in 1953 from chicken liver. It is a 622 amino acid-long protein [39–41]. Subsequently, in 1963, the 640 amino acid-long protein PEPCK-C, also known as PEPCK1 or *PCK1*, was discovered in mouse livers [40–42]. The *PCK1* gene is located on human chromosome 20q13.31 (PEPCK-C), while the *PCK2* gene is located on human chromosome 14q11.2 [43].

PCK1 and *PCK2* have 10 exons and 9 introns in humans, mice, and rats [44]. Their sequences share 82% similarity and 68% identity [40]. PCK1 mRNA has a very short half-life (30 min), while *PCK2* has a longer half-life. The tissues that express *PCK1* at the highest levels are adipocytes, proximal tubular epithelia of the kidney, hepatocytes, and intestinal epithelia [40].

PCK1 has potential patterns for binding carboxylate groups, Mn ions, ribose, guanine, and other molecules, as well as an active site that is 288 amino acids long. The binding pocket that includes guanine- and ribose-binding sites can accommodate the GTP nucleotide. To carboxylate group-binding sites, OAA and PEP bind [45]. It also contains transcriptional factor binding sites: cAMP response element (CRE), Glucocorticoid response element (GRE), thyroid response element (TRE), insulin response element (IRE), and PPAR response element (PPARRE) [46]. *PCK* regulates the production of glucose, fatty acid re-esterification, and citric acid cycle anions; it is important in maintaining energy homeostasis [8]. Other studies, however, have implicated additional non-canonical roles for *PCK-1*.

2.1.3. Functions of Pepck beyond gluconeogenesis

2.1.3.1. Glyceroneogenesis. Triglycerides (TG) are the primary source of lipids and energy. The breakdown of TG into one glycerol and three fatty acid molecules is known as lipolysis. The fatty acid is then changed into acetyl-CoA to fuel the Krebs cycle and create ATP [47]. Pyruvate can be converted into glyceroneogenesis, a process that maintains the triglyceride/fatty acid cycle, to create glycerol 3-phosphate, a required precursor of TG [48]. Glyceroneogenesis, which is a condensed version of it, shares several gluconeogenic enzymes [24,25].

The same is true for gluconeogenesis, where PCK1 is the rate-limiting enzyme. It catalyzes the conversion of OAA to PEP in adipose and liver tissues, which results in the formation of glycerol-3 phosphate [49]. Due to PEPCK-C overexpression, mice's adipose tissues experienced increased rates of glyceroneogenesis. On the other hand, when PEPCK-C expression in adipose tissue was reduced, animals with lipodystrophy were created [50].

2.1.3.2. PCK 1 and amino acid. PCK likely participates in anaplerosis and cataplerosis involving amino acids because it diverts TCA intermediate metabolites into the cytosol [9]. Specifically, for glycine and proline, PEPCK overexpressing cells show significant anabolic activity and increased amino acid consumption from culture media [8]. Amino acid byproducts are broken down, enter TCA, and are then converted into PEP, which is catalyzed by PCK and fed into the pathway that produces serine. This is necessary for cell growth and proliferation [51].

One crucial cataplerotic action of PEPCK-C is the recycling of citric acid cycle anions back into the cycle to create energy. This process adds carbon from amino acids to the citric acid cycle. In the mitochondria, the amino acid carbon is then further digested to create malate, which is further oxidized to oxaloacetate. Through PEPCK-C, phosphoenolpyruvate is transformed from oxaloacetate into pyruvate, which is then converted into acetyl-CoA in the mitochondria via the pyruvate dehydrogenase complex [52]. Acetyl-CoA can be utilized to synthesize fatty acids in the liver and is a substrate for complete oxidation in the citric acid cycle [53].

It has been suggested that some of the glutamine carbon consumed by the renal cortex engages in the same kind of carbon cycling via PEPCK-C [54].

Accordingly, the conversion of the citric acid cycle anion through oxaloacetate to phosphoenolpyruvate by PEPCK offers a high degree of metabolic flexibility because tissues like the skeletal muscle or small intestine can convert phosphoenolpyruvate to pyruvate and use this compound's consequent oxidation as acetyl-CoA in the citric acid cycle to produce energy [55]. Given all the above PCK1 activity, this review will give insight into the oncogenic or proto-oncogenic function imparted to PCK1 in cancer cells.

2.2. Regulation of PCK 1 in normal and cancer cells

PCK1 gene expression and transcription are regulated by hormones, nutrition, and post-translational changes. Insulin, glucagon,

glucocorticoids, and growth hormone are the hormones that control pck1 [56]. Insulin for instance, works by activating the phosphoinositide 3-kinase/Akt serine/threonine protein kinase (PI3K/Akt) signaling pathway in high glucose conditions. Subsequently, Fox head box protein 01 (FOXO1) and cyclic adenosine monophosphate regulatory element binding protein (CREB)-regulated transcription cofactor 2 (CRTC2) are activated by phosphorylation. This in turn causes FOXO1 (by its binding partner, a 14-3-3 protein), CRTC2 nuclear exclusion, and cytoplasmic retention. As a result, no phosphorylation or activation occurs on the transcription factor CREB. Finally, it reduces PCK1 expression by inhibiting *PCK1* messenger RNA (mRNA) transcription [57].

On the other hand, a polypeptide hormone secreted by alpha cells of the pancreas, glucagon, upregulates the expression of *PCK1* genes at the time of glucose deprivation. It acts by binding to its hepatic receptor, which is activated by conformational change [58]. As a result of the activated glucagon receptor, adenylate cyclase produces cAMP, the second messenger, which in turn promotes cAMP-dependent protein kinase (PKA), which phosphorylates the cAMP-response element-binding protein (CREB). The transcription of the *PCK1* gene is activated when phosphorylated CREB binds the cAMP response element (CRE) on it [56,59].

Glucocorticoids, such as cortisol, are steroid hormones that stimulate the gluconeogenic pathway in the liver by activating PCK1 while suppressing it in adipose tissue. The nuclear translocation of the glucocorticoid receptor (GR) is accelerated by ligand binding, and the gluconeogenic gene (*PCK1*) is subsequently activated [60]. Furthermore, growth hormone activates the Janus kinase/signal transducers and activators of the transcription 5 (JAK2/STAT5) pathway, which activates the PEPCK-C promoter [61].

Post-translational modifications involve acetylation, deacetylation, phosphorylation, and ubiquitination. While there is a high glucose concentration, PCK1 is acetylated by p300 acyltransferase [62]. This induces the anaplerotic function of PCK1 by directly affecting its kinetic properties. Furthermore, this acetylation facilitates chaperon-mediated degradation of PCK1 by improving its interaction with the ubiquitin-protein ligase E3 component N-Recognin 5 (UBR5 E3) ligase [63,64]. Simultaneously, PCK1 phosphorylation, mediated by glycogen synthase kinase 3 (GSK3), was discovered to promote ubiquitination and degradation in the presence of high glucose concentrations. In contrast, when there is a lack of energy, serine adjacent to Lys91 is phosphorylated. This results in PCK 1 deacetylation dependent on Silent Information Regulator-1 (SIRT 1) [65]. Generally, the cataplerotic and anaplerotic activities of *PCK1* have been elucidated to be regulated by crosstalk between phosphorylation, acetylation, and ubiquitination processes in the metabolism [65].

In cancer cells, there is no notable hormonal regulation of PEPCK. Tumor cells prefer to use post-translational modifications to hijack the enzymatic function of PCK 1. Acetylation, deacetylation, and SUMoylation are the proposed regulatory mechanisms in cancer cells [55].

3. Roles of PCK1 in cancer cell metabolism, proliferation and metastasis

3.1. Metabolism of cancer

Tumorigenesis is a multifaceted, intricate process that ultimately leads to unrestricted cell proliferation and expansion. The tumors' complex metabolic rewiring to suit their needs for energy and metabolite biosynthesis was found to be the primary mechanism underlying tumorigenesis [66].

A change in numerous metabolic pathways, including the serine-glycine and pentose phosphate pathways, as well as several rate-limiting enzymes in the glycolytic system, such as hexokinase 2, pyruvate kinase, and lactate dehydrogenase, stimulate glycolysis and offer clues for pro-survival in cancer cells. As a result, this strong glucose avidity paves the way for metabolic flexibility in cancer cells to have sustainable growth and proliferation [67]. Otto Warburg proposed this mechanism by which cancer cells cope with deprivation of energy by altering sugar metabolism, and called the Otto Warburg effect. It is an anaerobic breakdown of glucose even in the presence of oxygen and intact mitochondria [68,69]. Emerging studies have shown that cancer cells fulfill their metabolic requirements by hijacking gluconeogenic enzymes, particularly the PCK enzyme [70].

3.2. Roles of PCK1 in cancer

It is widely believed that PCK1 is a gluconeogenic enzyme and that it performs no major tasks when blood glucose levels are high. However, both PCK genes are expressed more frequently in several organ malignancies, including those of the colon, lung, and skin, which are linked to higher anabolic metabolism and cell proliferation [71].

PCK2, for instance promotes the survival of colorectal cancer by increasing TCA fluxes and breast cell carcinoma by increasing the concentration of PEP up on the deprivation of glucose [72,73]. On the other hand, RCC proliferation, metastasis, and invasion were decreased by PCK2 overexpression, while the expression of energy metabolites was increased [74].

It is controversial whether *PCK1* has a tumor suppressor or oncogenic role in different types of human malignancies. *PCK1* exhibits tumor-promoting effects in non-gluconeogenic organ malignancies, but anti-tumorigenic effects in gluconeogenic organ cancers (liver and kidney) [55]. The hijacking role and processes of *PCK1* in malignancies such as colon, hepatocellular carcinoma, breast, kidney, etc. have been clarified by several investigations.

Several studies have shown how much gluconeogenesis occurs in hepatocarcinomas. Ma et al. looked into this using the murine hepatocarcinoma tumor cell line H22, where lactate levels increase while *PCK1* is downregulated and unaffected by fasting. Also, they discovered that increasing *PCK1* expression prevented tumor growth. They discovered that the downregulation of the NADPH-dependent enzyme 11-hydroxysteroid dehydrogenase type 1 (11-HSD1) and the upregulation of the NAD + -dependent enzyme 11-HSD2—both of which are regulators of glucocorticoid (GC) activities that enhance the gluconeogenic synthesis of glucose by acting on *PCK* and G6Pase is increased by the knockdown of this enzyme [15].

In keeping with this, a study by Liu et al. revealed *PCK1* deletion dramatically increased cell proliferation in liver cancer lines, which is comparable to tumor suppressive function in vivo. Despite having significantly less expression in hepatocellular carcinoma (HCC), *PCK* genes seldom experience mutation [4,5]. Additionally, decreased *PCK1* expression was connected to a poor prognosis and may act as a stand-alone prognostic indicator for patients with high-risk HCC. This is because decreased *PCK1* expression was correlated with clinicopathological features such as tumor stage, tumor grade, and nodal metastasis status in HCC patients [75].

It was suggested that the downregulation of *PCK1* in HCC may be caused by FOXO1 depression caused by Hepatitis B virus X-interacting protein (HBXIP)-mediated *PCK1* promoter repression. By raising the expression of microRNA-135a (miR-135), which targets the 3' untranslated regions (3' UTR) of FOXO1 mRNA and enhancing its nuclear exclusion, HBX1P decreased FOXO1 expression in hepatoma cells. This encourages nucleotide synthesis, which provides a favorable environment for the development of cancer [76].

Similar to this, recent research has revealed that *PCK1* deficiency promotes protein O-linked N-acetylglucosamine acylation (O-GlcNAcylation) in hepatoma cells, which in turn causes HCC growth under low glucose conditions. This encourages oxaloacetate (OAA) and the AMPK-Glutamine-Fructose-6-phosphate transaminase 1 (GFAT1) axis-mediated uridine diphosphate-N-acetylglucosamine (UDP-Glc-NAc) production [77]. Meanwhile, it was discovered that PCK1-downregulated HCC cells have increased glucose use but decreased glucose production [78]. Nuclear factor erythroid 2-related

factor 2 and Kelch-like ECH-associated protein 1 (Nrf2/Keap1) are activated when *PCK1* is downregulated. This maintains a favorable environment for the development of hepatic tumors [79]. However, increased PCK1 expression negatively regulates cell cycle progression and hepatoma cell proliferation through the AMPK/cyclin-dependent kinase inhibitor 1B (p27Kip1) axis [80,81]. Consequently, when developing an anti-HCC medication, this finding would be important to consider.

Similar to this, *PCK1* is downregulated in clear cell renal cell carcinoma (ccRCC) cells, and it has been discovered that its overexpression stops these cells from proliferating, migrating, and invading [82,83]. Studies suggests that the *PCK1*/lactate dehydrogenase A (LDHA) axis prevents glycolysis in cancer cells [84]. On the other hand, *PCK1* increases colorectal cancer cell proliferation by encouraging the TCA cycle's use of glutamate and glucose [9].

The *PCK1* transcript was also found to be more expressed in the colon cancer cell line, according to Ref. [85]. Additionally, it has been hypothesized that treating pancreatic cancer with human pancreatic cancer tissues and cells that have high *PCK1* expression might be a possibility [86]. Moreover, the metalloproteinase enzyme-9/RAS/ERK/JNK/MMP-9 signaling pathway via SIRT-2 elevates the concentration of *PCK1*. This initiates the metastatic spread of gastric cancer [71].

Research revealed that *PCK1* is highly expressed and accelerates the development of breast, colon, lung, and pancreatic cancer by boosting the TCA cycle's use of lactate [87–89]. Thus, it was demonstrated that pharmacologically suppressing PCK, which also lowers lactate use, decreases the proliferation of tumor cells both in vitro and in vivo [88]. Through encouraging pyrimidine production, the overexpression of *PCK1* is also suggested to maintain colorectal cancer spread and tumor growth [90]. Moreover, *PCK1* did not stimulate gluconeogenesis in Tumors Repopulating melanoma Cells (TRCs); rather, it enhances serine, glycerol-3-phosphate, and other glucose side-branch metabolism. Retrograde glucose carbon flow increased rather than decreased glucose uptake and glycolysis. *PCK1* inhibition or silencing inhibited the growth of TRC in vitro and decreased cancer in animals [91].

The elevation of *PCK1* encouraged the production of neuroendocrine markers that are beneficial for the development of castration-resistant prostate cancer's (CRPC's) neuroendocrine features. Leukemia-inhibitory factor (LIF)/zinc finger LIF signaling activation regulates PCK1 and neuroendocrine marker expression through the BTB domain-containing 46 (ZBTB46) transcription factor [92]. Hence, when *PCK1* is addressed, prostate cancer cells can grow more slowly and display fewer neuroendocrine traits both in vitro and in vivo [92]. Table 1 provides an overview of *PCK1*'s impact on various malignancies.

Table 1
Summary of effects of PCK1 in some cancers.

Types of cancer	Effect	Suggested mechanism (reference)
Hepatoma cells	Impede tumorigenesis	Wnt signaling pathway [93]. Enhancing oxidative damage, apoptosis, and TCA cataplerosis [4,5,81]; [79]
ccRCC	Reduced ccRCC cell proliferation and metastasis in vitro and prevented tumour development in nude mice.	Causing post-translational modification of LDHA [84]
Colon cancer	Favours tumorigenesis Maintain CRC liver metastasis	Induce anabolic pathway [9] Promote nucleotides synthesis [90]
Lung cancer	Promote tumour progression	Triggers SREBP 1 [94]
Gastric cancer	Alleviate GC metastasis	Enhance the uptake of glucose, and glutamine, and increase TCA activity [71]
Prostate Cancer	Maintain cell proliferation	Stimulate LIF/ZBTB46 signaling [92]
Melanoma	Replenish a tumour	Enhance glycolysis, enabling the downstream carbon flow to serine and G-3-P [91].

4. Signalling and metabolic pathway associated with PCK1 roles in cancer

4.1. Enhanced glycolysis and glutaminolysis

Under nutrient-poor conditions, lipids can also act as a source of energy for cancer cells, enabling them to persist [95]. Accordingly, PEPCK's capacity to encourage lipid production aids in the coordination of a crucial aspect of cancer metabolism. Similarly, it maintains nucleotide, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) synthesis in tumor cells by enhancing glutaminolysis as well as utilization of glucogenic amino acids and the pentose phosphate pathway. It was also demonstrated that inhibition of glutaminolysis seldom affects cells expressing PEPCK, given that PCK1 has a protective effect [9].

The mechanisms used by *PCK1* to increase glutamine and glucose uptake include activation of the mammalian target of rapamycin complex 1 (mTORC1), enhancement of the production of matrix metalloproteinase 9, and up-regulation of extracellular signal-regulated kinase 1/2 activity [55].

4.2. Enhanced pyrimidine synthesis

By promoting aspartate synthesis, the precursor of pyrimidine, through reductive carboxylation, PEPCK1 tends to promote tumor growth in a hypoxic environment [90,96]. During this malate-aspartate shuttle, aspartate is exported to the cytoplasm and converted to OAA, which can then be reduced to malate [97]. Once inside the mitochondria, malate can be transformed back into OAA and provide the electron transport chain with reducing equivalents to support the highest possible rate of ATP generation. This shuttle is well recognized to be quite active in a variety of tumor cell lines [98].

It is unclear how PEPCK1 contributes to aspartate synthesis biochemically, however, it has been hypothesized that in the absence of pyruvate kinase in bacteria, PCK1 might function in reverse, converting phosphoenolpyruvate to oxaloacetate. The rise in phosphoenolpyruvate in hypoxic circumstances up to PCK1 inhibition supports this as well [90].

4.3. Lipogenesis by phosphorylating INSIG1/2

The membrane-bound transcription factors known as sterol regulatory element-binding proteins (SREBPs) control the transcription of genes required for the synthesis of fatty acids and cholesterol as well as the uptake of cholesterol. It includes the isoforms SREBP-1a, SREBP-1c/ADD1, and SREBP-2 [99]. Its regulation requires binding to the SREBP cleavage-activating protein (SCAP) [100]. This combination allows SREBP to move from the ER to the Golgi apparatus and cleaves its amine group, which then moves into the nucleus and stimulates the production of the lipogenic gene [101]. Increased intracellular sterol levels increase the quantity of cholesterol in the ER membrane, causing SCAP to alter conformation and bind to the products of insulin-induced genes (INSIGs), keeping the SREBP-SCAP complex in the ER [102].

The two INSIG isoforms, INSIG1 (277 amino acids) and INSIG2 (225 amino acids), both feature six transmembrane-spanning portions but distinct cytosolic N-termini [103].

INSIG proteins cannot bind cholesterol. Instead, they attach to oxysterols, which are cholesterol derivatives, such as 22-, 24-, 25-, and 27-hydroxycholesterol, in the central cavities of their transmembrane domains. INSIGs can interact with SCAP via transmembrane domains 3 and 4. The interaction between INSIGS and SCAP, which does not bind to oxysterols, is dependent on the binding of oxysterols to INSIGs. When lipids are depleted, INSIGS are released from SREBP and increase its

activation [3]. Consequently, AKT-mediated phosphorylation of PCK1 at S90 resulted in less phosphoenolpyruvate production during gluconeogenesis [3]. S90-phosphorylated PCK1 enters the ER and acts as a protein kinase, phosphorylating Insig1 S207 and Insig2 S15 with GTP as a phosphate donor, activating SREBP1 [94,104]. This, in turn, increases the synthesis of fatty acids and lipids [105].

4.4. AMPK/P27KIP1 axis

An energy sensor known as 5′-adenosine monophosphate (AMP)-activated protein kinase (AMPK) is activated by phosphorylation at Thr127 by downstream kinases like calcium calmodulin-dependent protein kinase 2 (CaMKK2) and liver kinase B1 (LKB1) as well as by allosteric activation via AMP binding in response to a lack of energy or adenosine triphosphate [106]. It inhibits the process of gluconeogenesis by phosphorylating class IIA histone deacetylases and CREB-regulated transcription coactivator 2 AMPK [56,107]. The AMPK signaling system has been demonstrated to successfully regulate autophagy, apoptosis, and proliferation. AMPK can directly induce autophagy by phosphorylating uncoordinated-51-like kinase 1 (ULK1) (or indirectly by inhibiting mTOR complex 1 by phosphorylating tuberous sclerosis complex 2 and/or raptor) when energy is scarce [108–110].

AMPK has also been shown to regulate apoptosis in part by phosphorylating the Cyclin-dependent kinase inhibitor 1B protein (p27Kip1) and to block the cell cycle by upregulating p27Kip1 [111]. p27Kip1 is a protein encoded by CDKN1B on chromosome 12p13 that is activated by phosphorylation [112]. Its phosphorylation includes a variety of variables and locations, depending on the desired result. AMPK, for example, phosphorylates it at Ser83 and Thr198, which aid in the retention of p27Kip1 in the cytosol, whereas Thr198 phosphorylation initiates autophagy [113]. In cancer, active p27Kip1 participates in various signal transduction pathways and regulates either a tumor suppressor or oncogenic actions, halting the cell cycle by inhibiting the cyclin E/CDK2 protein [113]. In general, p27KIP1 suppresses cyclin/CDK activity in the nucleus, hence inhibiting tumor growth [114].

Surprisingly, emerging studies showed the ability of PCK1 to activate AMPK independent of the upstream kinase that activates p27Kip1 and results in cell cycle arrest via inhibiting the Cyclin-dependent kinase-Retinoblastoma-E2 transcription factor (CDK/Rb/E2F) signaling pathway in cancer, particularly HCC, by holding the G1–S phase transition [80].

4.5. PCK1/LDHA axis

The glycolytic enzyme lactate dehydrogenase A (LDHA) catalyzes the oxidation of nicotinamide adenine dinucleotide hydrogen (NADH) to nicotinamide adenine dinucleotide (NAD+). By raising the rate of glycolysis, LDHA promotes the uncontrolled development of cancer cells, which in turn raises lactate generation [115].

Furthermore, LDHA promotes glucose uptake by increasing the synthesis of glucose transporter 1, a key glycolysis enzyme that delivers glucose into tumor cells via the phosphorylated AKT pathway [116]. As a result, it has been discovered that PCK1 inhibits cancer cell proliferation and growth by boosting chaperone-mediated autophagy (CMA)--dependent degradation of LDHA in specific malignancies [84].

4.6. Serine and glycerol-3-phosphate metabolism

As a one-carbon donor in the folate cycle, serine is essential for producing nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), which is necessary for methylation reactions, antioxidant defense, and nucleotide synthesis. Two cutting-edge treatment strategies involve inhibiting de novo serine production or decreasing the availability or uptake of exogenous serine [51].

The rate-limiting enzyme of serine synthesis, phosphoglycerate dehydrogenase (PGDH), catalyzes the conversion of 3-phosphoglycerate, into 3-phosphohydroxypyruvate [109,110]. Consequently, several malignancies regulate PCK1 expression and employ it as a promoter of serine biosynthesis response to external cues transmitted by V3 integrin to sustain metabolite deprivation in their environment [91].

4.7. LIF/ZBTB46-Driven glucose metabolism pathway

A transcription factor Zinc finger and BTB domain-containing protein 46 (Zbtb46) is a member of the broad complex, tram-track, bric-a-brac, and zinc finger protein families. It is profoundly expressed in quiescent dendritic cells and is the main regulator of gene transcription [117,118]. LIF, a member of the interleukin-6 (IL-6) family of cytokines, was first discovered in murine myeloid leukemia as a differentiation inducer and proliferation inhibitor [119].

However, additional studies revealed that LIF is expressed by a wide range of distinct cell lines and that this has a wide range of downstream consequences. In addition to serving as a neuropoietic cytokine and an important regulator of stem cell differentiation, the use of a particular LIF receptor controls the self-renewal of embryonic stem cells. It activates the RAS/mitogen-activated protein kinase (MAPK) and Janus kinase/STAT pathways [120]. At critical junctures in the development of the central nervous system, LIF plays a vital role in pancreatic cancer's ability to induce neuronal plasticity [120]. Moreover, LIF promotes migration and neuroglial cell differentiation by activating JAK/-STAT3/AKT signaling, and LIF signaling is commonly inappropriately active in advanced metastatic malignancies [118,119]. By direct binding to the LIF-regulatory region, activation of the LIF/STAT3 signaling cascade, and modulation of LIF expression, ZBTB46 regulates NE development in patients undergoing androgen deprivation therapy (ADT) [121]. ADT may contribute to the development of a lipid-rich environment in prostate cancer (PCa) cells that phosphorylate PCK1, increasing ZBTB46's alteration and controlling its expression [92].

When LIF/ZBTB46 signaling is active, there is a direct interaction between ZBTB46 and the PCK1 gene, which raises PCK1 and promotes glucose metabolism [92]. As a result, it has been discovered that ZBTB46's overexpression of PCK1 via LIF causes tumor development and metastasis by encouraging glucose use and neuroendocrine differentiation [92]. The metabolic pathways regulated by PCK1 to enhance tumor development and metastasis are summarized in Fig. 1.

5. Experimental drugs that could target PCK1

Targeting this process as a cancer treatment seems possible given the significant role gluconeogenesis plays in the glucose-lactate-glucose or glutamine-lactate-glucose reservoir cycles. However, there has been little investigation done on drugs targeting phosphoenolpyruvate carboxy kinase as an anti-cancer treatment.

PCK Inhibitor chloro-N- 4- [(3-(cyclopropyl methyl) -1- (2-fluorobenzyl)-2, 6-dioxo-2,3,6,9 tetrahydro-1 H-purin-8-yl) methyl] phenyl-1,3-dimethyl-1 H-pyrazole-4-sulfonamide has been created, and several cell lines have demonstrated its anti-cancer benefits. It is competitive inhibitor of PCK 1 that competes with GTP and binds to GTP binding sites on PCK1 [122]. Additionally, according to pre-clinical validation study on this PCK inhibitor, it is found to impede tumor growth in mice by inhibiting PEPCK-M with no obvious toxicity or weight loss both in vitro and in vivo [123]. Surprisingly, anti-cancer therapy targeting PCK1 has not yet been investigated and/or established.

6. Conclusion and future perspectives

This critical gluconeogenetic enzyme, PCK 1, becomes crucial but has a paradoxical effect based on the origin of the tumor. Though some mechanisms have been stipulated, there is no clear mechanism proposed for its paradoxical effect.

Moreover, PCK1 has a diverse spectrum of expression and activity in

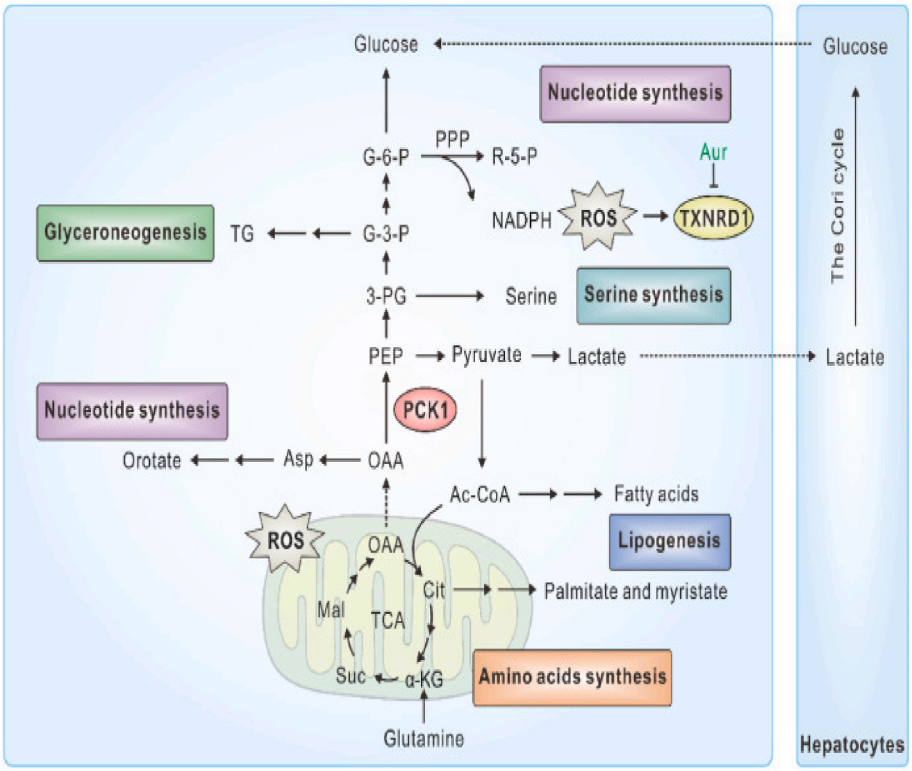

Fig. 1. Summary of metabolic pathways enhanced by PCK1 for tumorigenesis (adopted from [45]).

several tumors despite the tumor being in a non-gluconeogenic organ.

This could be related to the distinct needs of the disease for proliferation and metastasis, which would open the door and provide information for developing cancer-type-specific therapies.

Therefore, more cancer-specific PCK-1 genomic sequencing, structure, and expression, as well as its biochemical mechanisms and concentration in biological samples, needed to be investigated. That may help to understand its precise mechanism of action, and expression, as well as its understudied impact on metabolic rewiring in cancer. Moreover, it may help to develop a treatment that specifically and separately targets PCK1 in each cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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List of Abbreviation

11 β-HSD2	1β-Hydroxysteroid dehydrogenase type 2
11β-HSD1	1β-Hydroxysteroid dehydrogenase type 1
3'UTR	3'-untranslated regions
ADD1	Adipocyte Determination and Differentiation Factor-1
ADP	adenosine diphosphate
ADT	Androgen deprivation therapy
AMP	Adenosine monophosphate
AMPK	adenosine monophosphate kinase
cAMPK	Cyclic adenosine monophosphate kinase
CDK	Cyclin dependent kinase
CRE	cAMPK response element
CREB	cyclic adenosine monophosphate regulatory element binding protein
CRPC's	Castration-resistant prostate cancer
CRTC 2	CREB regulated transcription coactivator 2
E2F	Transcription factor 2
ERK	Extracellular signal regulated kinase
FOX01	Fox head protein 01
GC	Glucocorticoid
GDP	Guanosine Diphosphate
GFAT	Glutamine: fructose-6-phosphate aminotransferase
$GSK_3\beta$	Glycogen synthase kinase-3 beta
GTP	Guanosine Triphosphate
HBP	hexosamine biosynthetic pathway
IL	6-Interleukin-6
JAK2	Janus Kinase 2 gene
JNK	Jun N-terminal kinases
LDHA	Lactate dehydrogenase A
LIF	Leukocyte Inhibitory Factor
MAPK	Mitogen activating protein kinase
MiR	135a-Micro RNA 135a
MMP	9-Matrix Metalloproteinase-9
mRNA	messenger RNA
mTORC1	mammalian target of rapamycin complex 1
NAD^+	Nicotine Amide Dinucleotide
NADH	Nicotine Amide Dinucleotide hydrogen
NADPH	Nicotine Amide Dinucleotide Phosphate Hydrogen
PCK 2	Phosphoenolpyruvate carboxylase-2
PCK-1	Phosphoenolpyruvate carboxylase-1
PEPCK	Phosphoenolpyruvates carboxykinase

PHGDH	phosphoglycerate dehydrogenase
PKA	Protein Kinase A
Rb	Retinoblastoma
RNA	Ribonucleic Acid
SCAP	SREBP Cleavage Activating Protein
SIRT1	Silent information regulator 1
SIRT2	Silent information regulator 2
SREBP 1	Sterol regulatory element binding protein 1
SREBP-2	Sterol regulatory element binding protein 2
SREBP	sterol regulatory element binding protein
STAT3	Signal transducer and activator of transcription 3
STAT5	Signal transducers and activators of transcription 5
TCA	Tricarboxylic Acid Cycle
UBR5E3	ubiquitin-protein ligase E3 Component N-Recognin 5
UDP	Glc-NAc-mediated uridine diphospho-N-acetylglucosamine
ULK 1	Unc-51 Like Autophagy Activating Kinase 1
ZBTB46	Zink finger and BTB binding protein 46

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