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REVIEW

Proteins moonlighting in tumor metabolism and epigenetics

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Abstract **Cancer development is a complicated process controlled by the interplay of multiple signaling pathways and restrained by oxygen and nutrient accessibility in the tumor microenvironment. High plasticity in using diverse nutrients to adapt to metabolic stress is one of the hallmarks of cancer cells. To respond to nutrient stress and to meet the requirements for rapid cell proliferation, cancer cells reprogram metabolic pathways to take up more glucose and coordinate the production of energy and intermediates for biosynthesis. Such actions involve gene expression and activity regulation by the moonlighting function of oncoproteins and metabolic enzymes. The signal − moonlighting protein − metabolism axis facilitates the adaptation of tumor cells under varying environment conditions and can be therapeutically targeted for cancer treatment.**

Keywords moonlighting function; tumor metabolism; epigenetics

Introduction

Proliferation of cancer cell is restrained by nutrient accessibility in the tumor microenvironment. Cancer cells have to reprogram metabolic pathways to adapt to nutrient stress. Metabolic reprogramming is a hallmark of cancer and plays a vital role in the tumorigenesis and maintenance of malignancy [1]. Tumor cells take up more glucose and convert the majority of them to lactate even in the presence of oxygen compared with normal cells [2]. This phenomenon was first observed during a study on the metabolic reprogramming in cancer and was uncovered by Otto Warburg, hence its designation as the Warburg effect. It is exploited to detect tumor clinically by the combined use of ^{18}F-deoxyglucose and positron emission tomography (FDG-PET). Glutaminolysis, which involves glutamine utilization, is also upregulated in cancer cells. Aerobic glycolysis and glutaminolysis are two major metabolic alterations diverting carbon sources to biosynthesis to produce enough nucleotides, amino acids, and lipids for cell proliferation [3,4]. However, in non-glycolytic cancers, such as prostate cancer and B cell lymphoma, exogenous free fatty acids (FFAs) are oxidized to produce energy [5,6] and to promote tumor growth and metastasis [7,8]. Intriguingly, emerging evidence demonstrated that adipocytes and lipid metabolism are correlated with the drug resistance of cancer [9]. Iwamoto and colleagues found that anti-angiogenic drugs trigger lipid-dependent metabolic reprogramming, leading to increased FFAs and drug resistance. This anti-angiogenic drug resistance can be overcome by the suppression of fatty acid oxidation [10]. Despite these fascinating observations, the underlying mechanism by which cancer cells reprogram metabolic pathways according to metabolic signals remains elusive. Results of many studies have demonstrated that glycolysis and other metabolic alterations observed in multiple cancer types are governed by the moonlighting function of oncoproteins and metabolic enzymes to promote anabolism and support cell growth and proliferation [11–13].

Recently, several metabolic enzymes that possess canonical and moonlighting functions have been discovered [14–16]. Moonlighting proteins perform several independent and often unrelated noncanonical functions. Many oncoproteins and metabolic enzymes are moonlighting in tumor metabolism. The canonical regulation of oncoproteins to tumor metabolism occurs as a secondary

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response to nutrient stress and proliferation signals. The effector proteins need to be transcribed and translated before functioning. Moonlighting oncoproteins regulate metabolic flux as a primary response to metabolic stress and growth factor signaling associated with cell survival and proliferation, respectively, resulting in a more rapid and efficient response. Interestingly, most of the moonlighting proteins that regulate tumor metabolism are metabolic enzymes that directly sense metabolic signals and in turn activate gene expression through the regulation of transcription factor, DNA methylation, or histone acetylation. Here, we review proteins moonlighting in tumor metabolism and discuss their biological functions, translational implications, and research prospects.

Oncoproteins and tumor suppressor moonlighting in tumor metabolism

KRAS

The *RAS* oncogene family comprises more than 150 distinct members [17], and its signaling is frequently deregulated in tumorigenesis [18]. RAS proteins function as a molecular switch that cycles between active GTP-bound and inactive GDP-bound conformations [19]. RAS signaling controls many different cellular processes, such as cell proliferation, differentiation, and apoptosis [17]. Notably, multiple and recurrent gain-of-function mutations in *RAS* genes were identified in various types of human cancer, indicating that RAS signaling plays a fundamental role in tumor development [17,18]. Interestingly, not all RAS mutations occur at a similar frequency. The most commonly mutated *RAS* genes are *KRAS* (85%), *NRAS* (12%), and *HRAS* (3%) [19]. *KRAS* gene encodes two different protein forms (KRAS4A and KRAS4B) through alternative splicing [20]. Mutation of *KRAS*, mostly at G12, abolishes its GTPase activity and constitutively activates downstream signaling, leading to unconstrained cell proliferation, tumorigenesis, and tumor drug resistance [21].

Recent studies have found that oncogenic RAS promotes metabolic reprogramming of tumor cells to provide biomass support for uncontrolled proliferation by transcriptional upregulation of the glucose transporters and glycolytic enzymes, which increases glucose uptake and glycolytic flux even in the presence of oxygen; this is known as the Warburg effect [18,22,23]. Besides its canonical role in transmitting signals from extracellular growth factors to the cell nucleus, KRAS4A but not KRAS4B directly binds to and regulates hexokinase 1 (HK1), which is the initiating enzyme of glycolysis that catalyzes the transfer of a high energy phosphate group from ATP to glucose and produces glucose-6-phosphate in a GTP- and prenylation-dependent manner. Binding with HK1 on the outer mitochondrial membrane, KRAS4A represses the allosteric inhibition of HK1, thereby increasing its activity and enhancing glycolytic flux. Oncogenic KRAS4A has twice the effect of KRAS4B on the enhancement of the glucose consumption because of the unique function of KRAS4A on HK1 regulation [24], thereby providing a therapeutic target for patients bearing the KRAS oncogenic mutation (Fig. 1).

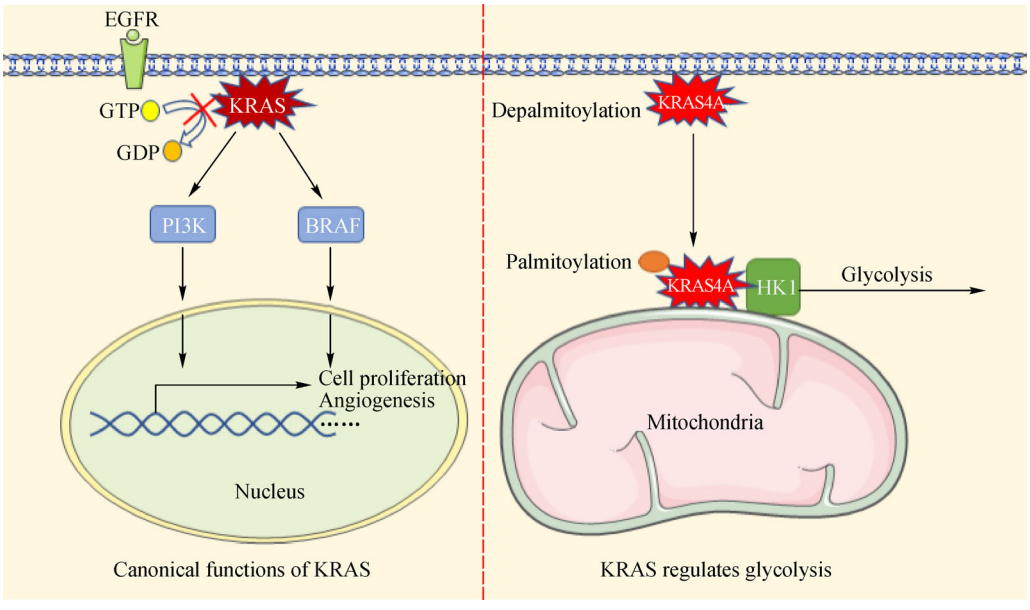

Fig. 1 The canonical and moonlighting functions of KRAS. The canonical (left panel) and non-canonical (right panel) functions of KRAS are summarized. Abbreviations: EGFR, epidermal growth factor receptor; GTP, guanosine triphosphate; GDP, guanosine diphosphate; PI3K, phosphatidylinositol 3-kinase; HK1, hexokinase 1.

p53

Tumor suppressor p53 serves diverse functions in multiple physiological and pathological processes, including cell cycle arrest, DNA repair, apoptosis, and senescence [25]. Besides its role in the nucleus as a transcription factor, p53 retains several moonlighting functions in the cytoplasm, especially in metabolic reprogramming. IKK-NF-κB is a canonical signal pathway in the regulation of cancer metabolism. p53 restricts glycolysis and the expression of glucose transporter GLUT3 by suppressing the activation of IKK-NF-κB pathway to inhibit cell transformation [26]. As the energy factory of cell, mitochondria plays a crucial role in cell metabolism. Cytosolic p53 promotes the permeability of mitochondria and triggers apoptosis through the activation of the pro-apoptotic factor Bax independent of its transcription activity [27]. Mdm2-mediated monoubiquitylation of p53 induces its mitochondrial translocation [28]. Being the guardian of mitochondrial genome, p53 interacts with CHCHD4 and POLG to enhance the repair of oxidative mtDNA damage and to maintain mtDNA integrity [29]. Glucose-6-phosphate dehydrogenase (G6PD) is the first and rate-limiting enzyme of the pentose phosphate pathway (PPP). p53 binds to G6PD and suppresses the formation of active dimer, thereby repressing glucose consumption, NADPH production, and biosynthesis. Tumor-associated p53 mutation abolishes its activity to inhibit G6PD, thereby enhancing PPP flux, increasing glucose consumption, and directing more glucose to biosynthesis to support the rapid growth and proliferation of tumor cells [30] (Fig. 2).

Signal transducers and activators of transcription 3 (STAT3)

STAT3 plays a key role in multiple biological processes, including cell growth, differentiation inflammation, and cancer development, depending on its function as a transcription factor [31–34]. Mechanistically, JAK kinases activate STAT3 via phosphorylation at Y705 residue upon cytokine or growth factor stimulation. Phosphorylated STAT3 forms homodimers, translocates into the nucleus, and activates target gene expression by binding to their promoter [35,36]. Besides serving as a transcription factor, a novel function of STAT3 in the mitochondria has also been discovered. Joanna Wegrzyn and colleagues found that STAT3 can get into the mitochondria and promote the activities of complexes I and II of the electron transport chain (ETC) and oxygen consumption, indicating the important role of STAT3 in regulating cell metabolism and maintaining cellular homeostasis independent of its transcriptional activity [37]. Subsequent studies further revealed the function of mitochondrial STAT3. STAT3 optimizes the function of ETC and regulates the opening of the mitochondrial permeability transition pore (mPTP), thereby manipulating the production of ATP and reactive oxygen species (ROS) and cell survival. Moreover, mitochondria STAT3 facilitates oncogenic transformation by increasing the ETC activity and sustaining altered glucose metabolism in cells [38] (Fig. 3). Therefore, targeting mitochondrial STAT3 function may be a promising treatment for cancer [38]. Recently, an inhibitor was developed to target mitochondrial STAT3 (mSTAT3). The binding of mSTAT3 with the inhibitor causes mitochondrial dysfunction and tumor death. Interestingly, the lethal consequence induced by mSTAT3 inhibition is enhanced by glucose starvation, which demonstrated the increase in sensitivity of cancer cells under metabolic stress to the mSTAT3 inhibitor; thus, mSTAT3 is a potential target for cancer therapy [39].

c-Myc

The proto-oncogene *c-Myc* is associated with many

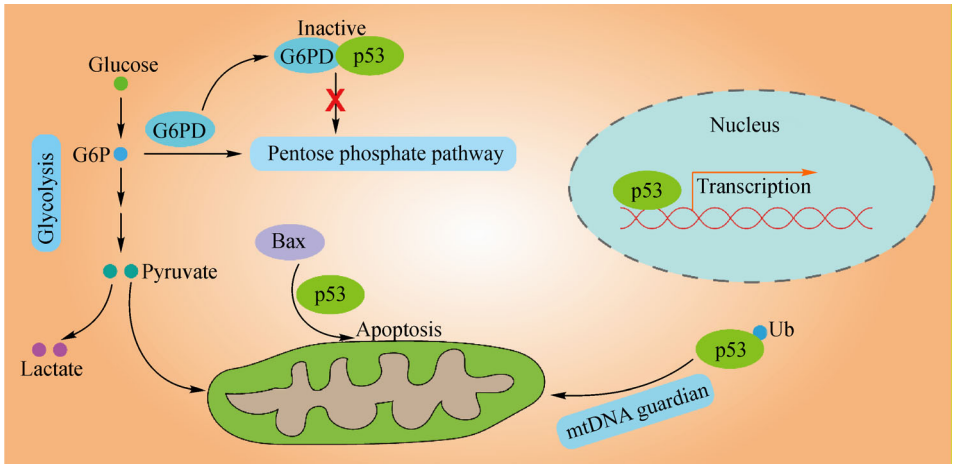

Fig. 2 The canonical and moonlighting functions of p53. The canonical and non-canonical functions of p53 are summarized. Abbreviations: G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; Bax, Bcl-2 associated X protein; Ub, ubiquitin.

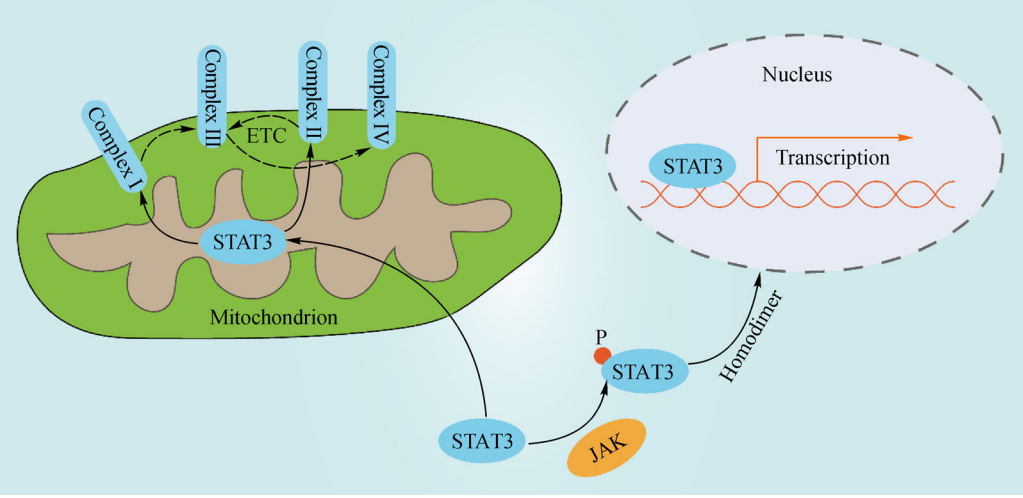

Fig. 3 The canonical and moonlighting functions of STAT3. The canonical and non-canonical functions of STAT3 are summarized. Abbreviations: STAT3, signal transducers and activators of transcription 3; JAK, Janus kinase.

physiological processes, such as cell cycle progression, apoptosis, and cell transformation [40]. *c-Myc* dysregulation occurs in more than 70% of tumors; it affects gene and microRNA expressions, genomic amplification, and the overall organization of nucleus [41]. The c-Myc protein forms a complex with MAX in the nucleus and promotes the transcription of target genes [42]. Overexpression of c-Myc causes genomic instability by increasing the phosphorylation at S139 of histone H2AX and forming γH2AX [43]. c-Myc can also reprogram metabolism in tumor cells, which induces metabolic stress and activates AMP-activated protein kinase (AMPK) [44–46]. c-Myc transcriptionally upregulates expression levels of glucose transporter 1 (GLUT1) and hexokinase 2 (HK2), as well as pyruvate kinase 2 (PKM2) through mRNA splicing, thereby increasing glycolytic flux and promoting tumor progression [47,48]. Besides its function in the nucleus, c-Myc cooperates with MCL1 to increase mitochondrial oxidative phosphorylation (mtOXPHOS), ROS production, and HIF-1α expression to contribute to the chemotherapy resistance of cancer stem cells (CSCs) in triple negative breast cancer. The suppression of HIF-1α restores chemotherapy sensitivity and inhibits CSC expansion [49].

Metabolic enzymes moonlighting in tumor metabolism

Aldolase (ALDO)

Aldolase (ALDO) is positioned midway in the glycolytic pathway and catalyzes the reversible cleavage of fructose-1,6-biphosphate (FBP) to dihydroxyacetone-3-phosopate (DHAP) and glyceraldehyde-3-phosphate (G3P) [50]. Three aldolase family members are involved in metabolism and glycolysis, namely, ALDOA, ALDOB, and ALDOC. Aldolase reportedly also plays a role in fructolysis. Fructose is catalyzed to fructose-1-phosphate by ketohexokinase and further converted to DHAP and glyceraldehyde by ALDOB and ALDOC [51]. ALDOA plays a major role in glycolysis and is highly expressed in several tumor types [52,53].

Besides its function as a glycolytic enzyme, recent studies demonstrated that aldolase can sense glucose level by binding to its substrate FBP. FBP-unoccupied aldolase binds to and suppresses ER-localized transient receptor potential V (TRPV) channels, thereby decreasing calcium level at the ER-lysosome contact, which in turn promotes the interaction of the channel proteins with lysosomal v-ATPase. Thus, the formation of a lysosomal complex containing v-ATPase, regulator, axin, liver kinase B1 (LKB1), and AMPK to induce AMPK activation is facilitated [14,54]. Once activated under low energy status, AMPK promotes ATP production by increasing the activity or expression level of proteins involved in catabolism and saves ATP by shutting down biosynthetic pathways, thereby contributing to the adaptation of cells to the nutrient limitation and the maintenance of energy homeostasis [55] (Fig. 4).

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

GAPDH is a conventional enzyme in glycolysis; it converts glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate and generates NADH [56]. GAPDH is reportedly involved in synthetic lethality in KRAS or BRAF mutant colorectal cancer. High dose vitamin C causes GAPDH S-glutathionylation and inactivation, leading to cell death, thereby suggesting that GAPDH may be a therapeutic target for colorectal cancer with KRAS or BRAF mutations [57]. GAPDH can bind to the AU-rich elements (AREs) in

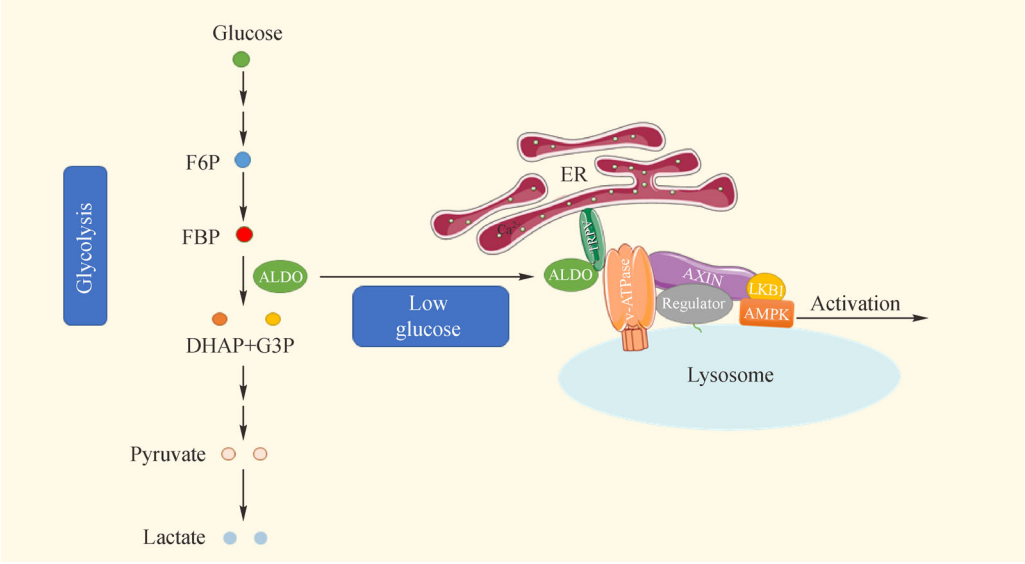

Fig. 4 The canonical and moonlighting functions of ALDO. The canonical and non-canonical functions of ALDO are summarized. Abbreviations: F6P, fructose-6-phosphate; FBP, fructose 1,6-bisphosphate; DHAP, dihydroxyacetone-3-phosopate; G3P, glyceraldehyde-3-phosphate; ER, endoplasmic reticulum; ALDO, aldolase; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase.

the 3′ UTR and destabilize the mRNA of vasoconstrictor endothelin-1 (ET-1). Interestingly, this process is also regulated by oxidative stress-induced S-glutathionylation of GAPDH. S-glutathionylated GAPDH cannot modify mRNA unwinding, thereby enhancing the mRNA stability of ET-1 [58].

In addition to its role in the cytoplasm, cytosolic GAPDH reportedly translocates into the nucleus in response to stresses and regulates physiological processes. Nitric oxide-induced S-nitrosylation at C150 induces GAPDH binding to Siah1 and initiates apoptosis [59]. Nuclear S-nitrosylated GAPDH transnitrosylates other nuclear proteins, such as SIRT1 and HDAC2, thereby suggesting that nitric oxide group transfer may represent a new signaling transmission mode [60]. The p300/CREB binding protein (CBP) acetylates nuclear GAPDH at K160, which in turn activates CBP and its downstream target *p53* to facilitate cell apoptosis [61]. During apoptosis, nuclear GAPDH cooperates with autophagy to protect caspase-independent cell death [62]. Under glucose starvation, GAPDH is phosphorylated at S122 by AMPK, leading to GAPDH nuclear translocation. Nuclear GAPDH stimulates SIRT1 activation and finally promotes autophagy to increase cell survival [63]. OCA-S is critical for S phase-dependent histone H2B transcription and may play a key role in cell metabolism. Nuclear GAPDH is a key component of OCA-S, whose function is stimulated by NAD^+ but repressed by NADH [64]. Apart from localization in cytoplasm and nucleus, free GAPDH protein transfers to the plasma membrane and forms a complex with transferrin, thereby becoming involved in iron metabolism [65] (Fig. 5).

Phosphoglycerate kinase 1 (PGK1)

PGK1 is a glycolytic enzyme that catalyzes the conversion of 1,3-bisphosphoglycerate (1,3-BPG) to 3-phosphoglycerate (3-PG) and produces ATP [66]. The activity and function of PGK1 are regulated by posttranslational modifications. Acetylation of PGK1 at K323 is reversibly regulated by P300/CBP associated factor (PCAF) and sirtuin 7 (SIRT7) and promotes the enzymatic activity and tumor metabolism of PGK1, thereby supporting tumor growth [67]. O-GlcNAcylation of PGK1 at T255 promotes PGK1 activity, lactate production, and mitochondria translocation, where PGK1 reduces oxidative phosphorylation by inhibiting pyruvate dehydrogenase (PDH), thereby promoting tumor growth [68]. Besides O-GlcNAcylation, phosphorylation of PGK1 also regulates its mitochondria localization. ERK phosphorylates PGK1 at S203 under oncogenic signal stimulation, which promotes its mitochondria translocation through PIN1-mediated cis-trans isomerization. Intriguingly, PGK1 acts as a protein kinase in the mitochondria and phosphorylates pyruvate dehydrogenase kinase 1 (PDK1) at T338, resulting in PDHK1 activation and phosphorylation and inactivation of PDH. These actions result in the blocking of pyruvate utilization in mitochondrial and ROS production and increase lactate production, thereby promoting Warburg effect to meet the needs of rapid proliferation of tumor cells by coordinating glycolysis and tricarboxylic acid (TCA) cycle [69]. Interestingly, PGK1 can also autophosphorylate and activate itself at Y324, thereby promoting glycolysis. Phosphatase PTEN dephosphorylates PGK1, thus suppressing glycolysis, ATP production, and tumor growth [70].

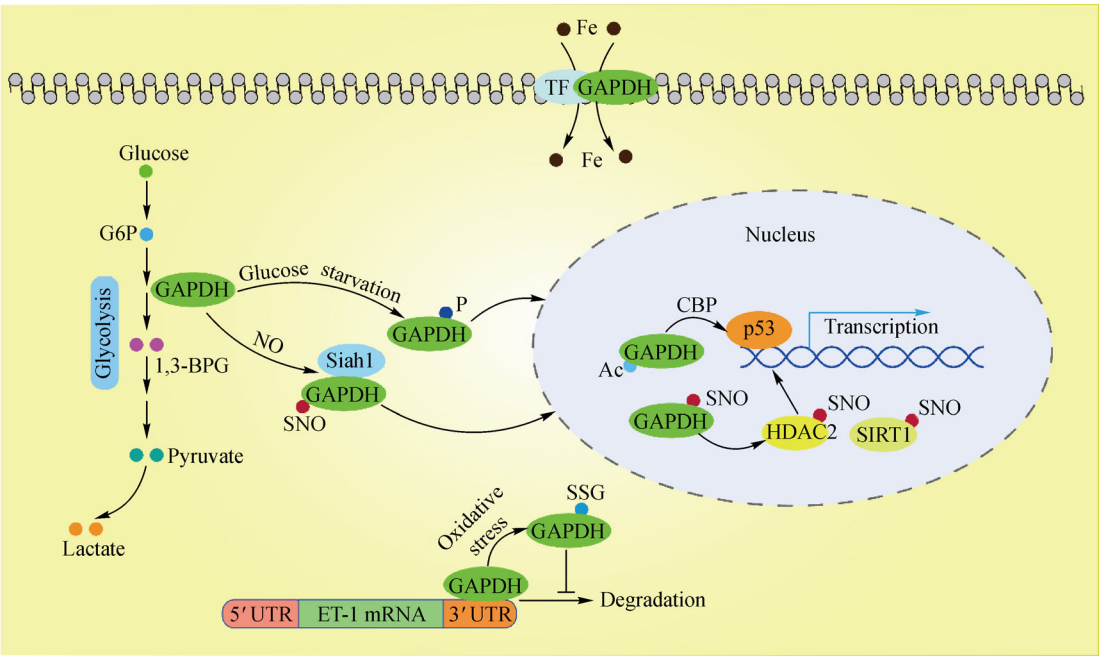

Fig. 5 The canonical and moonlighting functions of GAPDH. The canonical and non-canonical functions of GAPDH are summarized. Abbreviations: G6P, glucose-6-phosphate; 1,3-BPG, 1,3-bisphosphoglycerate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HDAC2, histone deacetylase 2; SIRT1, sirtuin 1; SNO, S-nitrosylation; SSG, S-glutathionylation.

S203 phosphorylation and T255 O-GlcNAcylation both mediate PGK1 mitochondrial localization, whereas all the modifications, including K323 acetylation, T255 O-GlcNAcylation, and Y324 phosphorylation, activate its enzymatic activity, thereby raising the question on whether these posttranslational modifications have crosstalk. S203 phosphorylation and T255 O-GlcNAcylation reportedly promote PGK1 mitochondrial translocation independently [68], but whether K323 acetylation, T255 O-GlcNAcylation, and Y324 phosphorylation have crosstalk is unclear. Possibly, these modifications enhance PGK1 activity collaboratively or they respond to different signals from the tumor microenvironment. These speculations require further investigation. In addition, under glutamine deprivation and hypoxia, PGK1 phosphorylates Beclin1 at S30, thereby enhancing VPS34-Beclin1-ATG14L complex activity, triggering autophagy, providing biomacromolecules for both energy production and biosynthesis, and maintaining the metabolism and homeostasis of tumor cells [71,72]. PGK1 reportedly translocates into the nucleus and functions as a transcription factor and driver of cell metastasis by repressing E-cadherin expression and metabolic reprogramming, thereby demonstrating that the subcellular localization of PGK1 creates a balance between proliferation and metastasis in SMAD4-negative pancreatic ductal adenocarcinoma [73] (Fig. 6).

Pyruvate kinase M2 (PKM2)

Pyruvate kinase regulates the final rate-limiting step of glycolysis, thereby catalyzing the conversion of phosphoenolpyruvate (PEP) to pyruvate and producing ATP. Pyruvate kinase has four isoforms, namely, PKL, PKR, PKM1, and PKM2. PKL, PKR, and PKM1 are expressed in specific tissues; the expression of PKM2 declines in a number of adult tissues but is highly upregulated in developing embryos and tumors [74–76]. The cytoplasmic function and regulation of PKM2 is crucial for tumor growth [77,78]. Tumor cells take up more glucose than normal cells. Under the stimulation of glucose at a high level, PKM2 is acetylated by PCAF at K305 and recruited by chaperone HSC70 to lysosome for degradation, thereby accumulating glycolytic intermediates for biosynthesis to support rapid tumor cell proliferation [79,80]. Among these isoforms, only PKM2 is detected in the nucleus, as it contains a nuclear localization signal (NLS), which is buried when it forms a tetramer and functions as metabolic kinase in the cytoplasm. PKM2 is acetylated by p300 acetyltransferase at K433, which is unique for PKM2, upon mitogenic and oncogenic signal stimulation, thereby preventing the binding of its allosteric activator, fructose-1,6-bisphosphate (FBP), and promoting tetramer-dimer transition, exposure of NLS, and translocation into the nucleus [81]. Phosphorylation also regulates the cytoplasm–nucleus translocation of PKM2. ERK2 binds to and phosphorylates PKM2 at S37 under EGF stimulation, which causes a conformational change, promotes PKM2 binding to importin α5 and translocation into the nucleus, and acts as a protein kinase [82,83]. PKM2 directly binds to and phosphorylates histone H3 at T11

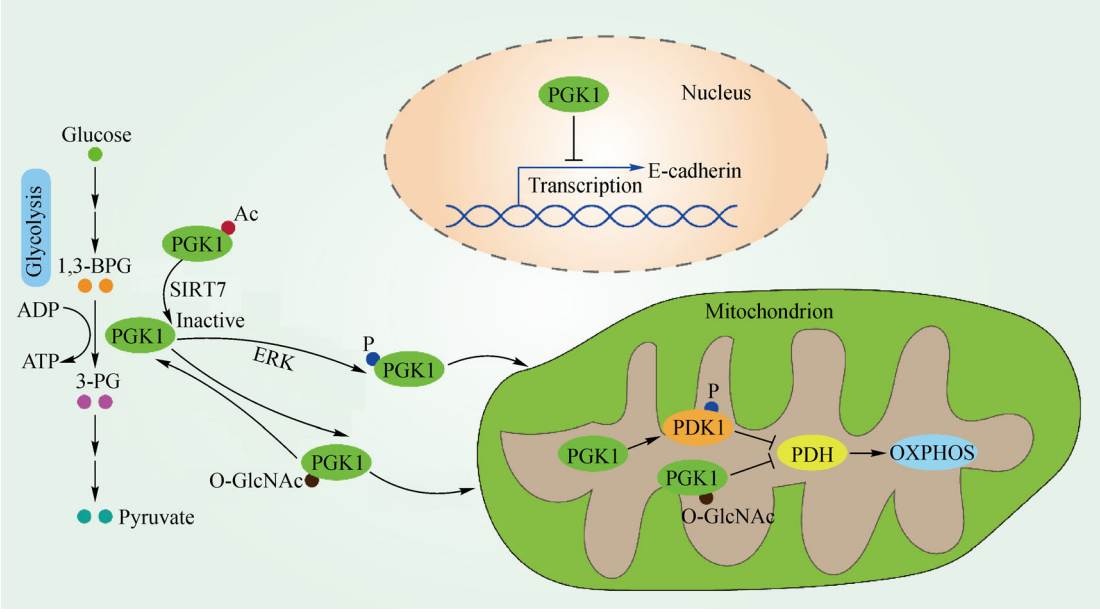

Fig. 6 The canonical and moonlighting functions of PGK1. The canonical and non-canonical functions of PGK1 are summarized. Abbreviations: 1,3-BPG, 1,3-bisphosphoglycerate; 3-PG, 3-phosphoglycerate (3-PG); ADP, adenosine diphosphate; ATP, adenosine triphosphate; PGK1, phosphoglycerate kinase 1; SIRT7, sirtuin 1; PDK1, pyruvate dehydrogenase kinase 1; PDH, pyruvate dehydrogenase; OXPHOS, oxidative phosphorylation; O-GlcNAc, O-GlcNAcylation.

using PEP as the phosphate donor, thereby enhancing the Warburg effect by upregulating the expressions of c-Myc target genes, such as glucose transporter type 1 (GLUT1) and lactate dehydrogenase A (LDHA) [82,84,85]. Moreover, nuclear PKM2 in the form of a dimer can also phosphorylate STAT3 at Y705 in the nucleus, promoting its transcriptional activity and activating MEK5 expression to promote cell proliferation and tumor growth [86,87]. Intriguingly, SAICAR, a metabolite abundant in proliferating cells, can bind to PKM2 and induce its protein kinase activity [88]. Besides its function as a protein kinase, nuclear PKM2 also serves as a co-transcription factor of HIF-1α and activates downstream target gene expression to reprogram tumor metabolism and promote tumor angiogenesis [89–92] (Fig. 7). Vander Heiden and others have not found PKM2 kinase activity under basal conditions [93]; their study is similar to ours, because we can only detect its protein kinase activity by stimulating with EGF [81]. Thus, more metabolic enzymes could potentially function as protein kinases under varied appropriate stimuli.

The dual function of PKM2 as a metabolic kinase and as a protein kinase is vital for tumor development. Thus, PKM2 inhibitors and activators are developed to treat tumors by distinct mechanisms [94–99]. PKM2 inhibitors promote tumor cell death by decreasing glycolytic flux and energy supply, whereas PKM2 activators suppress tumor cell proliferation by diverting glycolytic intermediates away from biosynthesis and inhibiting the nuclear function.

Fructose-1,6-bisphosphatase 1 (FBP1)

FBP1 is one of the rate-limiting enzymes in gluconeogenesis and converts fructose-1,6-bisphosphate to fructose-6-phosphate. However, many studies have demonstrated that FBP1 moonlights in tumor metabolism and functions as a tumor suppressor by decreasing glucose uptake, reducing glycolysis, and limiting cancer cell proliferation [100–103]; all these actions depend on its function in the nucleus. Nuclear FBP1 binds to and represses the activity of both HIF-1α and HIF-2α independent of its enzymatic activity, thereby decreasing the expressions of HIF target genes, such as *VEGF*, *GLUT1*, and *LDHA*, and suppressing tumor metabolism. Notably, nucleus-excluded FBP1 failed to inhibit tumor cell growth, indicating the importance of FBP1 moonlighting function [104]. In addition, FBP1 can bind to Notch1 and facilitates its proteasomal degradation, thereby reducing the expressions of Notch1 target genes and inhibiting breast tumorigenesis [105] (Fig. 8). FBP1 inhibits tumor metabolism and is a tumor suppressor. However, this is not always the case. In the lung tumor microenvironment, the high expression level of FBP1 in NK cells decreases glycolysis and viability, leading to the dysfunction of NK cells, which can be reversed by FBP1 inhibition [106].

Fructose-1,6-bisphosphatase 2 (FBP2)

FBP2 is the isozyme of FBP1 that shares 76.6% sequence

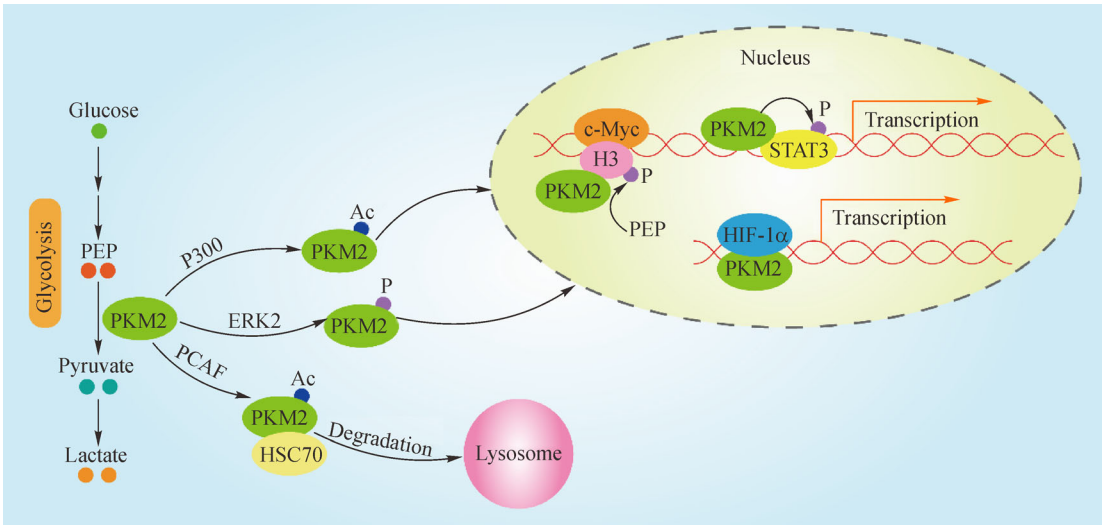

Fig. 7 The canonical and moonlighting functions of PKM2. The canonical and non-canonical functions of PKM2 are summarized. Abbreviations: PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; ERK2, extracellular signal-regulated kinase 2; HSC70, heat shock cognate 71 kDa protein; H3, histone H3; STAT3, signal transducers and activators of transcription 3; HIF-1α, hypoxia-inducible factor-1α.

identity with that in vertebrates. FBP1 is primarily expressed in the liver and kidney, whereas FBP2 is expressed more ubiquitously. Like FBP1, FBP2 suppresses a tumor and inhibits sarcoma progression independent of its function in gluconeogenesis, and these two actions involve two different mechanisms. FBP2 restrains enhanced glycolysis in cytoplasm, thereby inhibiting the Warburg effect and cell proliferation. Moreover, FBP2 translocates into the nucleus and binds to and suppresses c-Myc mediated *TFAM* expression, which in turn represses mitochondrial biogenesis and respiration independent of its enzymatic activity [15] (Fig. 8).

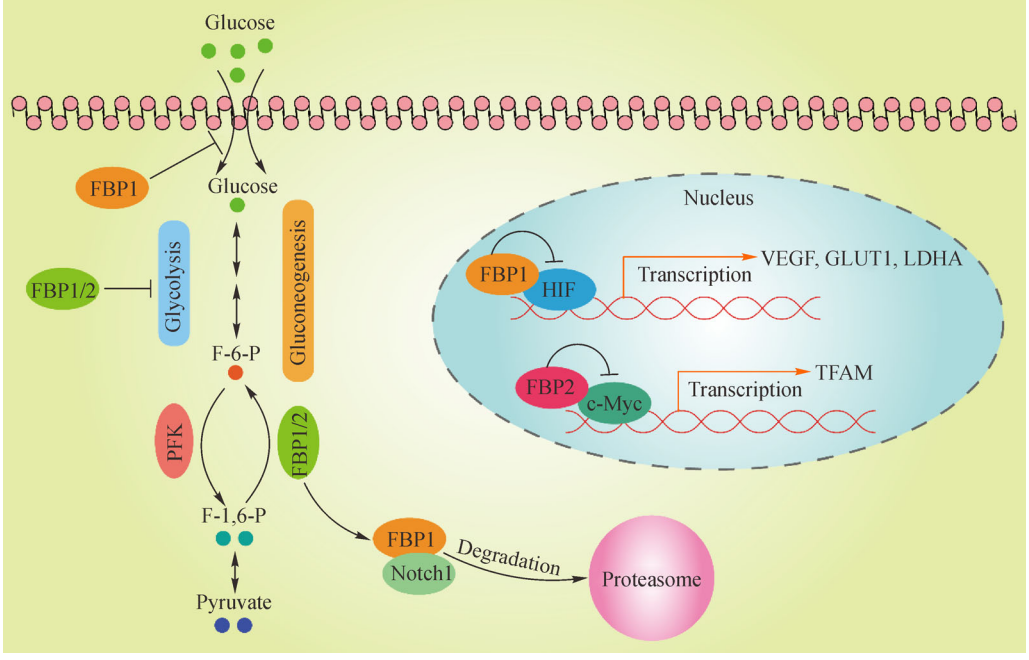

Fig. 8 The canonical and moonlighting functions of FBP1/2. The canonical and non-canonical functions of FBP1/2 are summarized. Abbreviations: F-6-P, fructose-6-phosphate; F-1,6-P, fructose-1,6-bisphosphate; FBP1/2, fructose-1,6-bisphosphatase 1/2; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; TFAM, transcription factor A, mitochondrial.

Phosphoenolpyruvate carboxykinase 1 (PCK1)

PCK1 is one of the rate-limiting enzymes of gluconeogenesis; it converts oxaloacetate and GTP to phosphoenolpyruvate and CO_2 [107]. PCK1 and its isoform, PCK2, shares 63.4% sequence identity and localizes in cytoplasm and mitochondria, respectively [108]. Rapid proliferative tumor cells require a large amount of amino acids, nucleosides, and fatty acids to synthesize proteins, DNA, and lipids. PCK1 reportedly shows protein kinase activity and promotes lipogenesis. Specifically, AKT phosphorylates PCK1 at S90 and promotes its translocation to the endoplasmic reticulum. In the endoplasmic reticulum, it phosphorylates INSIG1 at S207 and INSIG2 at S151, respectively, using GTP as the phosphate donor. This leads to the activation of SREBP proteins and the expression of genes required for lipogenesis. Thus, the proliferation of hepatocellular carcinoma (HCC) cells and tumorigenesis are promoted, demonstrating that the protein kinase activity of PCK1 is a promising target for the treatment of HCC [16].

Glutaminase (GLS) 1

Increased uptake and metabolism of glutamine is a hallmark of cancer. Glutamine is rapidly consumed to generate building blocks (amino acids, nucleotides, lipids, and carbohydrates) and energy (ATP) to support the growth and proliferation of cancer cells [1]. Glutamine also functions as a cell signaling molecule and promotes the synthesis of the antioxidant GSH [109]. GLS is the enzyme responsible for catalyzing the conversion of glutamine to glutamate, which is the first step of glutaminolysis. GLS has two isozymes, namely, GLS1 and GLS2. GLS1 is broadly expressed in various tissues and is highly expressed in many types of cancer. In contrast, the expression of GLS2 is restricted to the liver and brain [109].

Tumor development is challenged by nutrition limitation. Under glutamine deprivation, cancer cells undergo mitochondria fusion to promote the efficacy of respiratory chain and sustain the progression of tumor [110,111]. Cai *et al*. recently found that GLS1 can sense glutamine availability and initiates mitochondria fusion to help the cells overcome an energy crisis in an enzymatic activity-independent manner [112]. However, the detailed mechanism underlying this process has not yet been discovered.

Glutamate dehydrogenase (GDH) 1

GDH catalyzes glutamate to α-ketoglutarate (α-KG) and ammonia. α-KG is the key intermediate of the TCA cycle that interconnects amino acid and carbohydrate metabolisms [113]. There are two GDH isoforms in mammals, namely, GDH1 and GDH2. The expression of GDH1 is upregulated in multiple human cancers, including glioma, breast cancer, lung cancer, and leukemia [114,115], suggesting its function in tumor development. GDH1 manipulates intracellular fumarate level by controlling α-KG production. Fumarate in turn binds to and activates glutathione peroxidase 1 (GPx1) to scavenge ROS, thereby maintaining redox homeostasis and promoting tumor growth. Blocking GDH1 by a small molecule R162 leads to the imbalance in redox homeostasis and to the inhibition of cancer cell proliferation and tumor growth [116]. As the product of GDH1, α-KG plays a variety of roles in different metabolic and cellular pathways [117,118]. The loss of LKB1 in lung cancer is correlated to the increase in metastasis and poor prognosis. In LKB1-deficient lung cancer, α-KG activates CamKK2-AMPK signaling by increasing their binding, resulting in energy production, anoikis resistance, and tumor metastasis; thus, inhibiting GDH1 with R162 impairs tumor metastasis [119]. Under low glucose stimulation, AMPK phosphorylates GDH1 at S384, promoting its interaction with RelA and IKKβ. Thus, α-KG produced by GDH1 directly binds to and activates nuclear factor κB (NF-κB) signaling and upregulates GLUT1 expression, increasing glucose uptake and tumor cell survival [120,121] (Fig. 9). Collectively, GDH1 has unconventional functions in metabolic reprogramming through its product α-KG.

Ketohexokinase isoform A (KHK-A)

Ketohexokinase (KHK), also known as fructokinase, is the first rate-limiting enzyme in fructose metabolism. It catalyzes the conversion of fructose and ATP to fructose-1-phosphate (F-1-P) and ADP. F-1-P is then converted to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, which enter the later stage of glycolysis. KHK gene encodes two isoforms by alternative splicing, namely, KHK-A and KHK-C [122]. KHK-C is primarily expressed in liver, kidney, and intestines, whereas KHK-A is highly expressed in HCC cells and has a lower binding affinity to its substrate, fructose, than KHK-C; thus, KHK-A has a much lower activity than KHK-C [123,124].

c-Myc promotes the switch from the expression of KHK-C to KHK-A, resulting in much lower fructose catabolism rates, ATP consumption, and ROS production in HCC cells than in normal hepatocytes [125]. KHK-A interacts with and phosphorylates phosphoribosyl pyrophosphate synthetase 1 (PRPS1) at T225 in HCC cells, which activates PRPS1 by blocking the binding of its allosteric inhibitor ADP, leading to elevated *de novo* nucleic acid synthesis and HCC tumorigenesis through pentose phosphate pathway [125]. KHK-A is phosphorylated at S80, which is unique to KHK-A, by AMPK under oxidative stress. KHK-A in turn phosphorylates p62 at S28

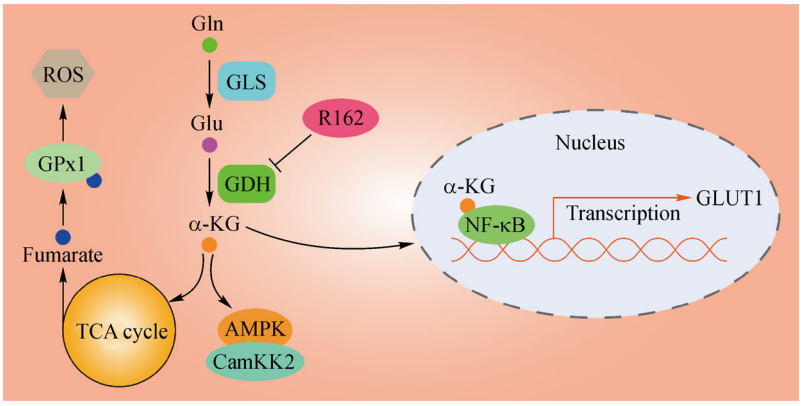

Fig. 9 The canonical and moonlighting functions of GDH. The canonical and non-canonical functions of GDH are summarized. Abbreviations: ROS, reactive oxygen species; GPx1, glutathione peroxidase 1; Gln, glutamine; Glu, glutamate; α-KG, α-ketoglutarate; GLS, glutaminase; GDH, glutamate dehydrogenase; AMPK, AMP-activated protein kinase; CamKK2, calcium/calmodulin dependent protein kinase kinase 2; NF-κB, nuclear factor κB; GLUT1, glucose transporter 1.

and prevents its ubiquitylation, thereby promoting gene expression via Nrf2 activation to reduce ROS and to promote cell survival and HCC development [126].

Metabolic enzymes moonlighting in regulation of epigenetics

Lactate dehydrogenase A (LDHA)

The Warburg effect is characterized by increased glucose uptake and lactate production, which is produced by LDHA by catalyzing pyruvate, and plays a vital role in the regulation of metabolic pathways [127]. LDHA is acetylated at K5, thereby decreasing its enzymatic activity and promoting its degradation via chaperone mediated autophagy (CMA), which reduces tumor cell proliferation and migration [128]. Reduction of LDHA activity affects glycolytic flux and stimulates oxidative phosphorylation, decreases mitochondrial membrane potential and inhibits proliferation of tumor cells under hypoxia [129]. LDHA uses pyruvate as substrate but also catalyzes α-ketobutyrate (α-KB) [130]. However, the product and significance of this reaction is unknown. The collaboration study between the Canhua Huang and Qunying Lei groups found that LDHA translocates into the nucleus in response to HPV16E7-induced ROS accumulation, where it gains a moonlighting function to convert α-KB to α-hydroxybutyrate (α-HB), thereby promoting histone H3K79 trimethylation and activating antioxidant gene expression and Wnt signaling pathway to maintain cellular redox balance and cervical cancer cell proliferation under oxidative stress [131]. Besides α-HB, LDHA and MDH convert α-KG to L-2-hydroxyglutarate (L-2-HG) at acidic pH, thereby stabilizing HIF-1α [132] (Figs. 10 and 11).

Isocitrate dehydrogenase 1/2 (IDH1/2)

Isocitrate dehydrogenase (IDH) catalyzes the oxidative decarboxylation of isocitrate to α-KG and produces NADPH [133]. IDH contains several isoforms, among which IDH1 and IDH2 are the most widely investigated and expressed in cytoplasm and mitochondria, respectively. Notably, IDH1 and IDH2 are frequently mutated in multiple tumors, including malignant gliomas [134,135], acute myeloid leukemia [136], cholangiocarcinoma [137], chondrosarcomas, and thyroid cancers [138]. Intriguingly, mutant IDH1/2 has gained the new function of converting α-KG to 2-HG [139–141], which accumulates in the tumor cells and inhibits multiple α-KG-dependent dioxygenases as a competitive inhibitor of α-KG, thereby leading to the dysregulation of histone and DNA demethylation to block cell differentiation and to promote tumorigenesis [142,143]. Elevated 2-HG level is observed in the serum of patients with IDH mutated glioma and acute myeloid leukemia, whereas the concentration of 2-HG is very low in normal tissues. 2-HG can be used as a biomarker for the clinical detection of cancer. mTOR is a key regulator of cancer metabolism. EGFR, NF1, and PTEN are upstream regulators of mTOR signaling pathway and are also frequently mutated in cancer. Interestingly, in the absence of EGFR/NF1/PTEN mutation, mTORC1/2 signaling is activated by IDH1/2 mutation and exogenous 2-HG, suggesting that 2-HG may regulate the activity of mTOR1/2 through an independent and non-canonical pathway to promote tumor cell survival and proliferation [144,145]. Besides histone and DNA demethylase, more than 60 other α-KG dependent dioxygenases reportedly exist, all of which could be inhibited by 2-HG; these include hypoxia inducible factors (HIF) and AlkB proteins that are responsible for the DNA repair of alkylation damage [146–148]. Thus, the oncometabolite 2-HG may

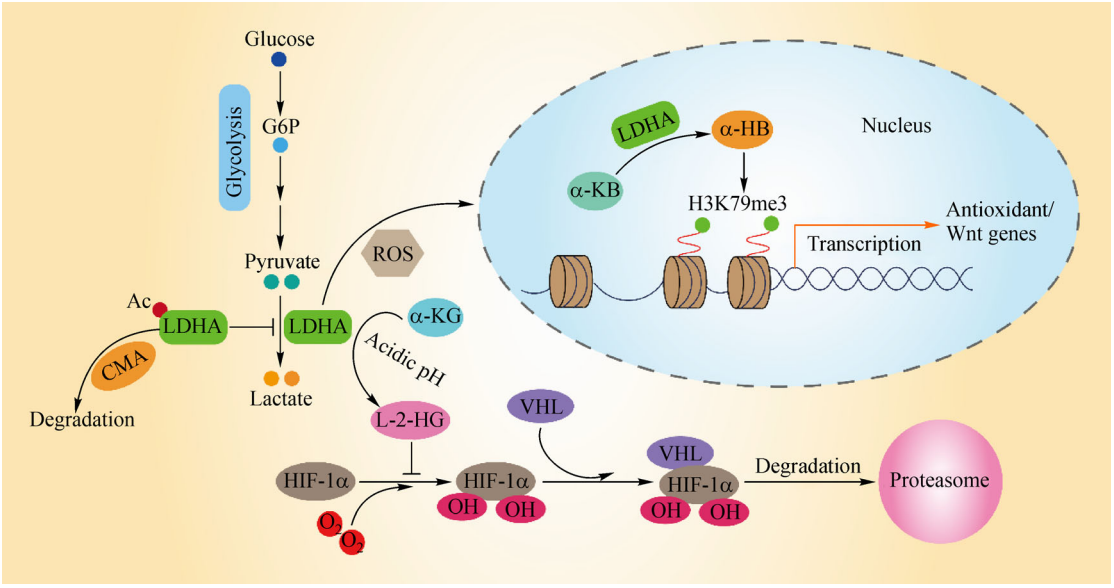

Fig. 10 The canonical and moonlighting functions of LDHA. The canonical and non-canonical functions of LDHA are summarized. Abbreviations: G6P, glucose-6-phosphate; LDHA, lactate dehydrogenase A; CMA, chaperone-mediated autophagy; ROS, reactive oxygen species; α-KG, α-ketoglutarate; α-KB, α-ketobutyrate; L-2-HG, L-2-hydroxyglutarate; HIF-1α, hypoxia-inducible factor-1α; O_2, oxygen; OH, hydroxylation; VHL, von Hippel-Lindau.

promote tumor development through multiple pathways, making mutant IDH a potential target for the reversal or relief of the biological consequences caused by 2-HG (Fig. 11).

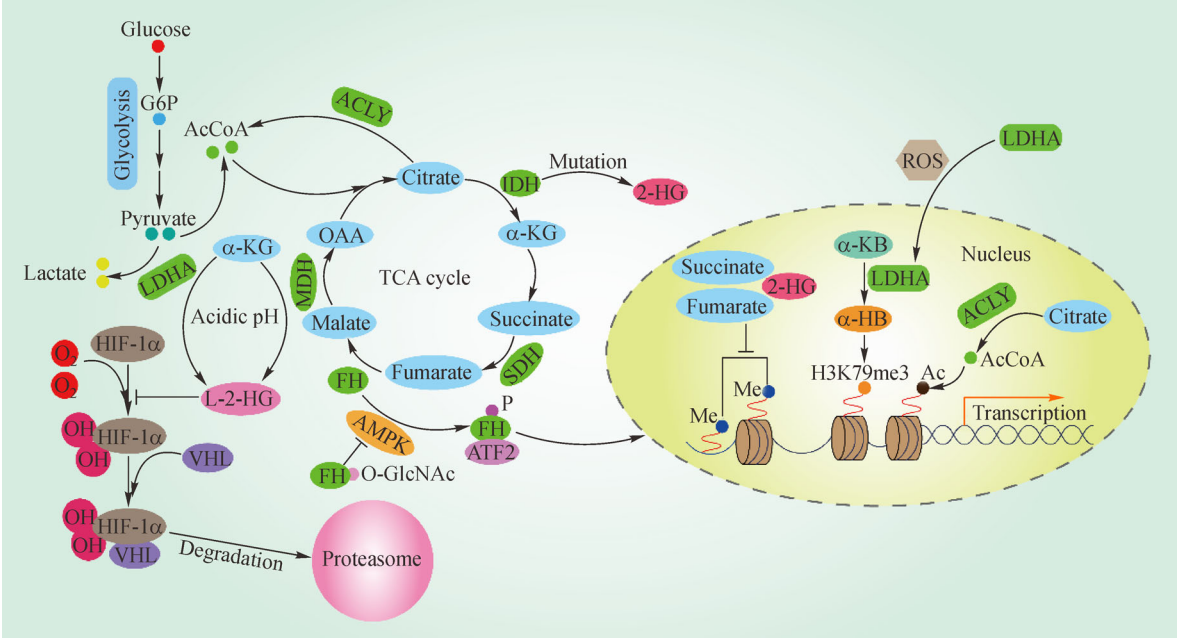

Fig. 11 Metabolic enzymes moonlighting in regulation of epigenetics. The metabolic enzymes regulating epigenetics are summarized. Mutations in IDH, SDH, and FH accumulate 2-HG, succinate, and fumarate, respectively, thereby suppressing DNA and histone demethylation. The α-KB and Ac-CoA produced by LDHA and ACLY, respectively, promote histone H3K79 tri-methylation and acetylation. LDHA and MDH can also convert α-KG to L-2-HG at acidic pH. Abbreviations: G6P, glucose-6-phosphate; LDHA, lactate dehydrogenase A; α-KG, α-ketoglutarate; α-KB, α-ketobutyrate; L-2-HG, L-2-hydroxyglutarate; HIF-1α, hypoxia-inducible factor-1α; O_2, oxygen; OH, hydroxylation; VHL, von Hippel-Lindau; ACLY, ATP-citrate lyase; MDH, malate dehydrogenase; IDH, isocitrate dehydrogenase; SDH, succinate dehydrogenase; FH, fumarate hydratase; O-GlcNAc, O-GlcNAcylation; ATF2, activating transcription factor 2; ROS, reactive oxygen species; Me, methylation; H3K79me3, H3K79 tri-methylation; Ac, acetylation.

Table 1 Summa ry of metabolic enzymes moonlighting in tumor metabolism and epigenetics

Metabolic process	Enzyme	Canonical function		Moonlight function in tumor metabolism and epigenetics	
		Location	Function	Location	Function
Glycolysis	ALDO	Cytoplasm	Converts fructose-1,6-biphosphate to dihydroxyacetone-3-phosopate and glyceraldehyde-3-phosphate	ER surface	Senses glucose availability through FBP binding and activates AMPK signaling under low glucose status [14,54]
	GAPDH	Cytoplasm	Converts glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate and generates NADH	Nucleus	S122 phosphorylation by AMPK promotes nuclear translocation, activates SIRT1, and promotes autophagy and cells survival under glucose starvation [63]
					Binds to OCA-S and increases histone H2B transcription, thereby affecting cell metabolism [64]
				Cell membrane	Forms a complex with transferrin and involved in iron metabolism [65]
	PGK1	Cytoplasm	Converts 1,3-bisphosphoglycerate to 3-phosphoglycerate and produces ATP	Mitochondria	Inactivates pyruvate dehydrogenase as a protein kinase, blocks pyruvate utilization and ROS production, and increases lactate production, thereby promoting the Warburg effect [69]
					T255 O-GlcNAcylation promotes mitochondria localization, inhibits the activity of pyruvate dehydrogenase, and reduces oxidative phosphorylation [68]
				Cytoplasm	Phosphorylates Beclin1 at S30 and triggers autophagy under glutamine deprivation and hypoxia [71,72]
				Nucleus	Functions as a transcription factor, drives cell metastasis via repression of E-cadherin expression and metabolic reprogramming [73]
	PKM2	Cytoplasm	Converts phosphoenolpyruvate to pyruvate and produces ATP	Nucleus	Phosphorylates histone H3, upregulates c-Myc target genes, such as GLUT1 and LDHA, to promote the Warburg effect [82,84,85]
					Phosphorylates STAT3 at Y705, promotes its transcriptional activity, and activates MEK5 expression to promote cell proliferation and tumor growth [86,87]
					Functions as a co-transcription factor of HIF-1α and activates downstream target gene expression to reprogram tumor metabolism [89–92]
	LDHA	Cytoplasm	Converts pyruvate to lactate	Nucleus	Converts α-ketobutyrate to α-hydroxybutyrate, which promotes histone H3K79 tri-methylation and activates antioxidant gene expression and Wnt signaling pathway to maintain cellular redox balance and cervical cancer cell proliferation [130,131]
				Cytoplasm	Gains new activity to convert α-KG to L-2-hydroxyglutarate (L-2-HG) at acidic pH, thereby stabilizing HIF-1α [132]
Gluconeogenesis	FBP1/2	Cytoplasm	Converts fructose-1,6-bisphosphate to fructose-6-phosphate	Nucleus	FBP1 binds to HIF and decreases the expressions of its target genes, such as VEGF, GLUT1, and LDHA, to suppress tumor metabolism [104]
					FBP1 binds to Notch1 and facilitates its degradation, thereby reducing the expressions of Notch1 target genes and inhibits breast tumorigenesis [105]
					FBP2 binds to and suppresses c-Myc-mediated TFAM expression, which in turn represses mitochondrial biogenesis and respiration [15]
	PCK1	Cytoplasm	Converts oxaloacetate and GTP to phosphoenolpyruvate and CO_2	ER	AKT-mediated PCK1 S190 phosphorylation functions as a protein kinase to phosphorylate INSIG1, leading to the activation of SREBP proteins and the expression of genes required for lipogenesis [16]

(*Continued*)

Metabolic process	Enzyme	Canonical function		Moonlight function in tumor metabolism and epigenetics	
		Location	Function	Location	Function
TCA cycle	IDH1	Cytoplasm	Converts isocitrate to α-KG and produce NADPH (wild-type) Converts α-KG to 2-hydroxyglutarate (2-HG) (mutant)	Cytoplasm	2-HG accumulates in tumor cells, leading to the dysregulation of histone and DNA demethylation to block cell differentiation and promotes tumorigenesis, thereby activating mTORC1/2 signaling in the absence of EGFR/NF1/PTEN mutation [144,145]
	IDH2	Mitochondria		Mitochondria	
	SDH	Mitochondria	Converts succinate to fumarate (wild type) Accumulates succinate (mutant)	Nucleus	Accumulated succinate competitively inhibits the α-KG-dependent dioxygenases, including histone demethylases and TET family of 5mC hydroxylases [151]
	FH	Mitochondria	Converts fumarate to L-malate (wild-type) Accumulates fumarate (mutant)	Nucleus	Accumulated fumarate competitively inhibits the α-KG dependent dioxygenases, including histone demethylases and TET family of 5mC hydroxylases [151]
					Inhibits KDM2B-mediated histone H3 K36 demethylation and promotes DNA repair and cell survival [13,152]
					O-GlcNAcylation of FH blocks AMPK-mediated phosphorylation; FH fails to form the FH-ATF2 complex and loses its transcriptional regulatory activity; tumor is maintained growth under glucose deficiency [153]
	MDH1	Cytoplasm	Converts malate to oxaloacetate	Cytoplasm	Gains new activity to convert α-KG to L-2-hydroxyglutarate (L-2-HG) at acidic pH, thereby stabilizing HIF-1α [132]
	MDH2	Mitochondria		Mitochondria	
Glutaminolysis	GLS1	Mitochondria	Converts glutamine to glutamate	Mitochondria	Senses glutamine availability and initiates mitochondria fusion to help the cells to overcome energy crisis under low glutamine status [112]
	GDH	Mitochondria	Converts glutamate to α-ketoglutarate and ammonia	Mitochondria	Manipulates the intracellular level of fumarate, which activates glutathione peroxidase 1 to scavenge reactive oxygen species, thereby maintaining redox homeostasis [116]
					In LK1-B deficient lung cancer, α-KG produced by GDH1 activates CamKK2-AMPK signaling, resulting in energy production [119]
					Under low glucose stimulation, α-KG produced by GDH1 directly activates NF-κB signaling, upregulates GLUT1 expression, and increases glucose uptake [120,121]
Fructose metabolism	KHK-A	Cytoplasm	Converts fructose to fructose-1-phosphate	Cytoplasm	Phosphorylates and activates PRPS1, thereby promoting *de novo* nucleic acid synthesis and HCC tumorigenesis through pentose phosphate pathway [125]
					KHK-A S80 phosphorylation phosphorylates p62 and prevents its ubiquitylation, thereby promoting gene expression via Nrf2 activation to reduce reactive oxygen species [126]
Others	ACLY	Cytoplasm	Converts citrate to acetyl-CoA	Nucleus	Under growth factor stimulation and cell differentiation, ACLY-generated acetyl-CoA promotes histone acetylation and gene expression [155,156]

Fumarate hydratase (FH)

FH, also known as fumarase, is a key mitochondrial metabolic enzyme in the TCA cycle [149]. The typical function of FH is catalyzing the reversible conversion of fumarate to L-malate [150]. FH and another TCA cycle enzyme, succinate dehydrogenase (SDH), which converts succinate to fumarate, are both mutated in cancer cells, resulting in the accumulation of their substrates, fumarate and succinate, respectively. Fumarate and succinate are competitive inhibitors of multiple α-KG dependent dioxygenases, including histone demethylases and the ten-11 translocation (TET) family of 5mC hydroxylases [151]. Nuclear FH is phosphorylated by DNA-PK at T236 and recruited to double-strand break (DSB) regions in response to ionizing radiation (IR), where it generates fumarate to locally inhibit KDM2B-mediated histone H3 K36 demethylation, which in turn promotes DNA repair and cell survival [13,152]. While under glucose deprivation, AMPK phosphorylates FH at S75, thereby promoting FH-ATF2 binding. The complex translocates into the nucleus and binds to the promoters of ATF2 target genes. FH-catalyzed fumarate locally inhibits KDM2A activity and thus maintains the H3K36me2 level to facilitate target gene expression and to promote cell growth arrest. Notably, O-GlcNAcylation of FH blocks AMPK phosphorylation site. FH fails to form the FH-ATF2 complex and loses its transcriptional regulatory activity in the nucleus, thereby maintaining tumor growth under glucose deficiency [153] (Fig. 11).

ATP-citrate lyase (ACLY)

ACLY converts citrate into acetyl-CoA and is upregulated in several types of tumor. Under high glucose conditions, ACLY is acetylated by PCAF at lysine K540, K546, and K554; the blocking of its ubiquitylation and degradation stabilizes ACLY and promotes *de novo* lipid synthesis, cell proliferation, and tumor growth [154]. Surprisingly, Wellen *et al*. demonstrated that ACLY-generated acetyl-CoA is the main source for histone acetylation in mammalian cells. Growth factor stimulation and glucose availability promote ACLY-dependent histone acetylation, which is required for the expressions of hexokinase 2 (HK2), phosphofructokinase-1 (PFK-1), lactate dehydrogenase A (LDH-A), and glucose transporter 4 (GLUT4). Therefore, knockdown of *ACLY* results in a 32% decrease of glucose consumption, which links growth factor and glucose availability to the regulation of histone acetylation and metabolic alteration [155,156] (Fig. 11).

Discussion

Approximately 19 000 protein coding genes are present in the human genome, but only hundreds of moonlighting proteins have been identified so far [157]. The number of moonlighting proteins will increase quickly, as the significance of protein moonlighting in biology and translational medicine is becoming increasingly apparent (Table 1). Study results have demonstrated that moonlighting proteins can execute novel biological functions, thereby broadening the pool of human functional proteome and simultaneously providing tumor cell growth advantage and therapeutic vulnerability.

Biological function: protein moonlighting provides rapid and efficient response to oncogenic mutations

Proteins moonlighting offers functional options for tumor cells to respond to metabolic stress without the transcription and translation of new proteins. Furthermore, some moonlighting proteins directly bind to metabolic enzymes and regulate their activity. For example, oncoprotein KRAS4A uniquely and directly binds to and activates HK1, thereby enhancing glycolytic flux [24]. Tumor suppressor p53 can also directly bind to G6PD and suppress its activity, thereby repressing glucose consumption, NADPH production, and biosynthesis. Intriguingly, tumor-derived p53 mutation abolishes its inhibition to G6PD, thereby enhancing PPP flux, promoting glucose consumption, and diverting more glucose to biosynthesis to support the rapid growth and proliferation of tumor cells [30]. These direct bindings provide rapid and efficient response to oncogenic mutations, which is important for the unconstrained proliferation of tumor cells.

Translational implication: protein moonlighting provides therapeutic vulnerability

Cancer cells reprogram metabolic pathways by protein moonlighting in response to external signals to support cell survival and proliferation, thereby providing a growth advantage and a therapeutic target for cancer treatment. Both the cytoplasmic and nuclear functions of PKM2 are important for cell growth and proliferation and are controlled by tetramer-dimer transition, thereby providing an excellent target for the treatment of cancer. PKM2 activator increases its metabolic activity in the cytoplasm, which diverts biomass away from biosynthesis, and inhibits protein kinase activity by promoting dimer–tetramer transition [98]. PKM2 is acetylated by p300 acetyltransferase at K433, and K433 acetylation acts as a switch for the shift of the metabolic and nuclear function of PKM2; thus, K433 acetylation is a promising target for cancer treatment [81]. Targeting p300 could increase its enzymatic activity and inhibit its nuclear function as protein kinase and co-transcription factor [158], thereby repressing tumor growth. The direct binding of KRAS4A to HK1 also can be targeted for patients bearing KRAS

oncogenic mutation to block the glycolytic flux. Exploring and targeting the moonlighting function is a promising strategy for the clinical treatment of cancer.

Research prospect: metabolites regulate signaling pathways

Cancer metabolism is regulated by multiple signaling pathways and vice versa. Metabolites provide feedback to coordinate signaling pathways to reprogram metabolism. α-KG generated by GDH1 plays an important role in the regulation of different cellular signaling pathways, such as activation of CamKK2-AMPK [119] and NF-κB pathways [120,121], to reprogram metabolism. Fumarate binds to and activates GPx1 to scavenge ROS and to maintain redox homeostasis [116]. As analogs of α-KG, 2-HG, fumarate, and succinate can potentially inhibit more than 60 α-KG-dependent dioxygenases, including histone and DNA demethylase, HIF, and AlkB proteins. Identifying new signaling pathways regulated by metabolites and checking whether 2-HG, fumarate, succinate, and α-KG could regulate CamKK2-AMPK, NF-κB, and GPx1 antioxidant pathways would be interesting.

More than 110 000 metabolites, nearly 3500 proteins related to metabolism dysregulation, and the tumor and metabolomics data of multiple tumors, including liver, breast, kidney, and colorectal cancers, are present in the Human Metabolome Database (HMDB). By means of bioinformatics, in-depth mining in the existing database would reveal the metabolic characteristics of different tumors, leading to the discovery of metabolic pathways and important metabolites closely related to tumor occurrence and development.

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Compliance with ethics guidelines

Lei Lv and Qunying Lei declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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