



Interplay Between Glucose Metabolism and Chromatin Modifications in Cancer

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Cancer cells reprogram glucose metabolism to meet their malignant proliferation needs and survival under a variety of stress conditions. The prominent metabolic reprogram is aerobic glycolysis, which can help cells accumulate precursors for biosynthesis of macromolecules. In addition to glycolysis, recent studies show that gluconeogenesis and TCA cycle play important roles in tumorigenesis. Here, we provide a comprehensive review about the role of glycolysis, gluconeogenesis, and TCA cycle in tumorigenesis with an emphasis on revealing the novel functions of the relevant enzymes and metabolites. These functions include regulation of cell metabolism, gene expression, cell apoptosis and autophagy. We also summarize the effect of glucose metabolism on chromatin modifications and how this relationship leads to cancer development. Understanding the link between cancer cell metabolism and chromatin modifications will help develop more effective cancer treatments.

Keywords: metabolism, epigenetic modifications, gene transcription, tumorigenesis, histone modifications

INTRODUCTION

Tumor cells need to change their metabolism to support their demands for rapid growth and proliferation, so called metabolism reprogram (Pavlova and Thompson, 2016). This metabolic reprogram enables cells to synthesize a large amount of precursors for biomacromolecule synthesis (Pavlova and Thompson, 2016). The extensively studied metabolic reprogram is aerobic glycolysis, also known as the “Warburg effect.” That is, cancer cells preferentially convert pyruvate, the end product of glycolysis into lactate instead of transporting pyruvate into the mitochondria for oxidative phosphorylation. Although aerobic glycolysis is a less efficient way to produce energy (2 ATP/glucose), it helps accumulate a large amount of metabolite precursors for biosynthesis of macromolecules, i.e., nucleic acids, fatty acids, and amino acids (Hanahan and Weinberg, 2011). Initially, the mitochondria in tumor cells was thought to have defects, which makes them unable to perform oxidative phosphorylation and highly dependent on glycolysis (Dang and Semenza, 1999). However, the function of mitochondria in most tumor cells is intact. Recent studies show that tumor cells mainly use the tricarboxylic acid (TCA) cycle in the G1 phase and prefer glycolysis in the S phase (Liu et al., 2021), suggesting that both TCA cycle and glycolysis are important for tumor cells.

Many metabolic enzymes and metabolites have non-metabolic functions in tumorigenesis, including regulation of chromatin modifications, gene transcription, DNA damage, etc. (Yu and Li, 2017). These non-metabolic functions provide useful clues to develop more efficient anti-cancer therapy. In this review, we described the functions of metabolic enzymes and

metabolites from glycolysis, gluconeogenesis, and TCA cycle in tumorigenesis with an emphasis on their non-metabolic functions. We also described how they are regulated and their effects on chromatin modifications.

METABOLIC REGULATION OF TUMOR CELL PROLIFERATION

The Role of Glycolytic Enzymes in Tumorigenesis

Hexokinase

Hexokinase (HK2) is the first rate-limiting enzyme in glycolysis, which is highly expressed in tumor cells and acts as a potential target for cancer treatment (Chen J. et al., 2014). HK2 binds to the mitochondrial membrane *via* its interaction with the outer membrane porin protein, voltage-dependent anion channel (VDAC) (Figure 1). VDAC is a critical channel that regulates the release rate of mitochondrial intermembrane pro-apoptotic proteins, such as cytochrome *c* (Linden et al., 1982). The interaction between HK2 and VDAC inhibits the release of intermembrane pro-apoptotic proteins, thereby protecting tumor cells from apoptosis (Figure 1) (Linden et al., 1982). HK2 has also been reported to interact with the mammalian target of rapamycin complex 1 (mTORC1) by binding to its subunit, regulatory-associated protein of mTOR (Raptor) (Figure 1) (Roberts et al., 2014). Upon glucose deprivation, HK2 directly binds to mTORC1 to inhibit its function and activate the protective autophagy pathway (Roberts et al., 2014).

The expression of HK2 is closely correlated to the occurrence of cancers such as laryngeal cancer and breast cancer, metastasis of breast cancer cells and poor prognosis of patients (Palmieri et al., 2009; Kwee et al., 2012; Min et al., 2013). HK2 expression is regulated by microRNAs, long non-coding RNA and various transcript factors. The expression of miR-143 is negatively correlated with the HK2 expression level in a variety of cancers, including prostate cancer, breast cancer, and head and neck squamous cell carcinoma (HNSCC) (Zhang et al., 2017). miR-143 directly targets the 3'UTR (3' untranslated region) of HK2 to repress its expression (Peschiaroli et al., 2013). miR-155 down-regulates the transcription of miR-143 by targeting its transcription activator C/EBP β , which then affects HK2 expression (Jiang et al., 2012). The long non-coding RNA UCA1 up-regulates HK2 transcription by repressing miR-203 and upregulated UCA1 enhances the malignant phenotype of esophageal cancer (Liu et al., 2020). HK2 is also regulated by transcription factors. For example, hypoxia-inducible factor 1 α (HIF-1 α) binds the promoter of HK2 to activate HK2 transcription, which accelerates glycolysis and facilitates cutaneous squamous cell carcinoma (cSCC) development (Zhou et al., 2018). In addition, the expression of HK2 is activated by transforming growth factor- β (TGF- β) and this activation requires transcription factors like Smad2, Smad3, and c-Myc (Yin et al., 2019).

Phosphoglucose Isomerase

Phosphoglucose isomerase (PGI) is the second glycolytic enzyme, which is highly expressed in a variety of tumor cells, including

human breast carcinoma BT-549 cells, human colon cancer cell HCT116, human bladder cancer cell J82 (Tsutsumi et al., 2004, 2009; Funasaka et al., 2009). In lung cancer patients, high PGI expression is associated with poor prognosis and reduced survival rate (Funasaka et al., 2005). The activity of PGI1 can be inhibited by small molecules, i.e., the glucose analog, 2-deoxy-D-glucose (2-DG) (Figure 1) (Pusapati et al., 2016). The small molecule inhibitor, Esculetin can directly bind PGI and repress its activity, which triggers apoptosis and inhibits tumor growth (Wu S. T. et al., 2020).

PGI also acts as an autocrine motility factor (AMF) in tumor progression and metastasis (Funasaka et al., 2005). Its receptor, AMFR/gp78 is overexpressed in multiple tumors and correlated with poor prognosis (Pusapati et al., 2016). It is known that PGI/AMF can function as an anti-apoptotic factor. PGI/AMF down-regulates the expression of apoptotic protease activating factor-1 (Apaf-1) and caspase-9 genes to reduce apoptosis (Haga et al., 2003). In addition, PGI/AMF can reduce apoptosis by activating the PI3K/Akt signaling pathway (Figure 1) (Fruman and Rommel, 2014).

Phosphofructokinase 1

Phosphofructokinase 1 (PFK1) catalyzes the conversion of fructose-6-phosphate into fructose-1,6-bisphosphate. PFK1 has 3 isoforms: platelet (PFKP), muscle (PFKM) and liver (PFKL), among which PFKP is the major PFK1 isoform and overexpressed in human glioblastoma cells (Mor et al., 2011). PFK1 facilitates tumor growth as knockdown of PFK1 inhibits the migration and proliferation of colorectal cancer (Lang et al., 2019).

The activity of PFK1 is regulated by different covalent modifications. For example, PFKP can be acetylated by lysine acetyltransferase 5 (KAT5) at lysine 395 (K395) upon activation of the epidermal growth factor receptor (EGFR) (Lee et al., 2018). Acetylated PFKP then translocates into the plasma membrane, where it is phosphorylated by EGFR at tyrosine 64 (Y64) to enhance its activity (Lee et al., 2018). PFKP can also be phosphorylated by AKT at serine 386 (S386), which protects PFKP from degradation and facilitates tumor growth (Lee et al., 2017). Under anaerobic conditions, PFK1 is modified by O-linked β -N-acetylglucosamine (O-GlcNAc) at serine 529 (S529) (Yi et al., 2012). Glycosylation of PFK1 reduces its activity and diverts the glucose flux into the pentose phosphate pathway (PPP), resulting in a significant increase in NADPH, which promotes the proliferation and tumorigenicity of lung cancer cells (Yi et al., 2012).

Aldolase

Aldolase catalyzes the conversion of fructose 1-6-diphosphate to glyceraldehyde 3-phosphate and dihydroxy-acetone phosphate. Aldolase has three tissue-specific isozymes: ALDOA (muscles), ALDOB (liver) and ALDOC (neuronal tissue) (Lincet and Icard, 2015). Among these isozymes, ALDOA is overexpressed in a series of cancers, including colorectal cancer, hepatocellular carcinoma, lung cancer, and pancreatic cancer and promotes tumor growth, invasion, and migration (Du et al., 2014; Shimizu et al., 2014; Ji et al., 2016; Kawai et al., 2017). Mechanistically, ALDOA activates the EGFR/MAPK pathway to

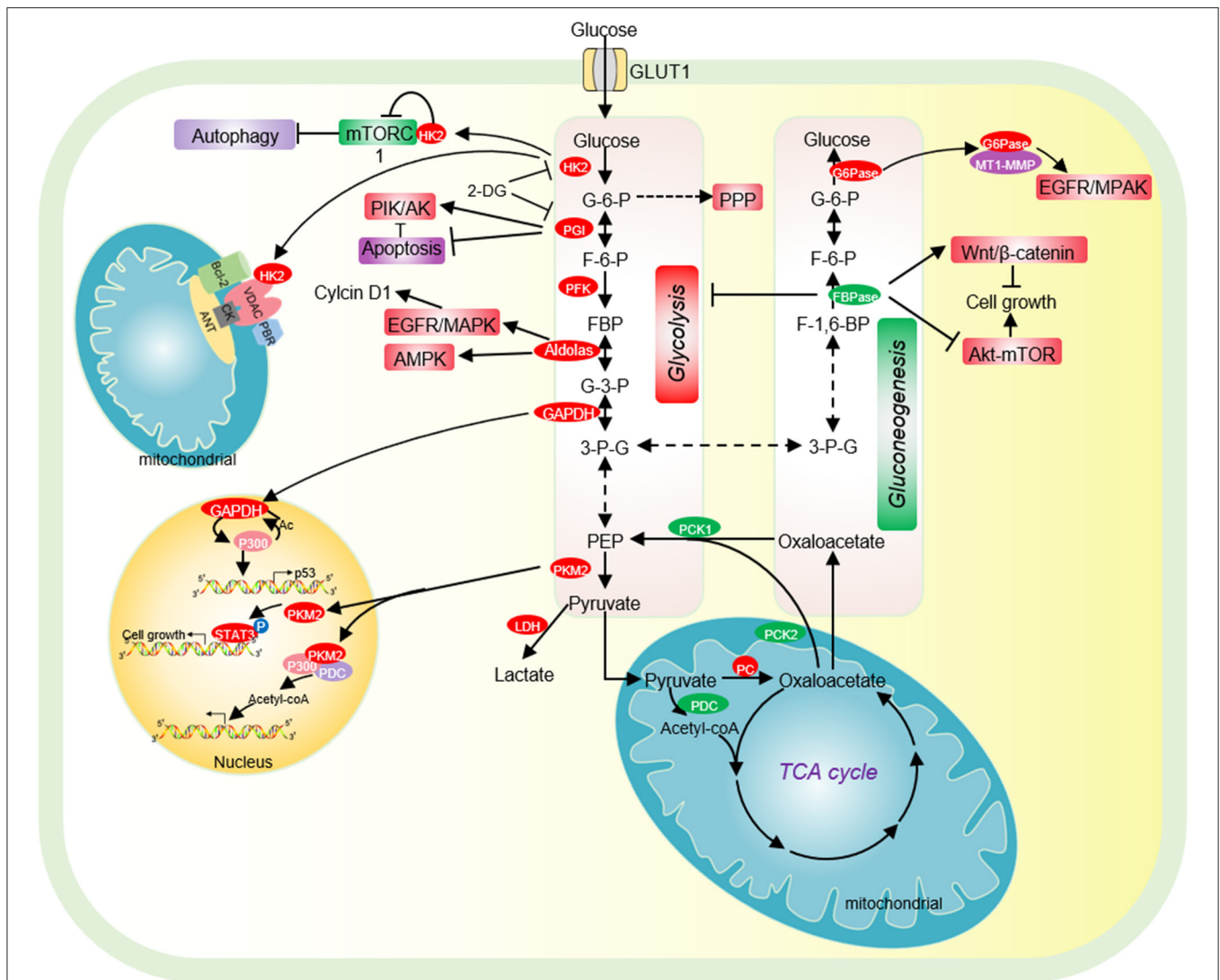
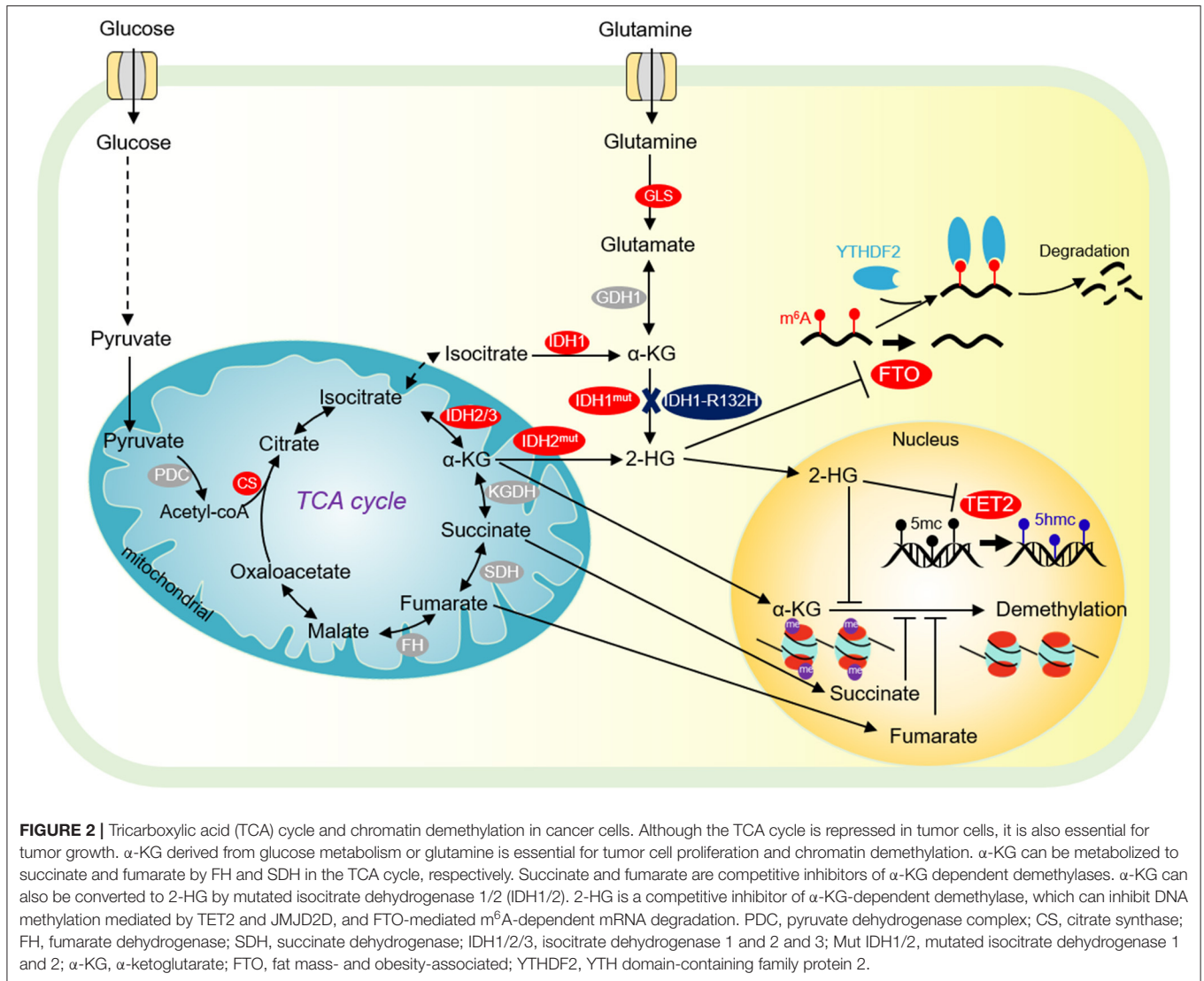


FIGURE 1 | The effect of glycolysis and gluconeogenesis on tumor cell proliferation. Cancer cells have increased glucose uptake, leading to accelerated glycolysis and biomass accumulation. The high expression of GLUT1, HK2, PGI, PFK, Aldolase, GAPDH, and PKM2 significantly accelerates aerobic glycolysis. Increased lactate dehydrogenase (LDH) activity and decreased pyruvate dehydrogenase (PDC) activity result in increased lactate export, attenuated TCA cycle and diversion of glycolysis to pentose phosphate pathway (PPP). HK2 not only directly binds to mTORC1 to activate autophagy, but also interacts with VDAC to protect tumor cells from apoptosis. PGI inhibits cell apoptosis by inhibiting the expression of Apaf-1 and caspase-9 and activating the PI3K/Akt signaling pathway. Acetylated nuclear GAPDH promotes tumorigenesis by activating p300 and promoting p53 expression. Aldolase promotes cell cycle progression through the EGFR/MAPK signaling pathway, and activates AMPK to maintain tumor cell survival in glucose deficiency. Nuclear PKM2 performs a variety of non-metabolic functions to promote cell cycle progression. Low expression of pyruvate carboxylase (PC), the key enzyme of gluconeogenesis, is essential for the proliferation of some cancer cells. PC is essential for the synthesis of fatty acid and glycerol in cancer cells. The low expression of the key enzyme PEPCK of gluconeogenesis is beneficial for the proliferation of cancer cells. FBPase acts as a tumor suppressor and inhibits the proliferation of tumor cells. G6PT promotes the invasion of glioblastoma by interacting with MT1-MMP. HK2, hexokinase 2; G-6-P, glucose-6-phosphate; PGI, phosphoglucose isomerase; F-6-P, fructose-6-phosphate; FBP, fructose-1,6-bisphosphate; G-3-P, glyceraldehyde-3-phosphate; 3-P-G, 3-phosphoglycerate; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; PKM2, Pyruvate kinase M2; LDH, lactate dehydrogenase; PC, Pyruvate carboxylase; PCK1/2, phosphoenolpyruvate carboxykinase 1/2; PDC, pyruvate dehydrogenase complex; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; FBPase, fructose-1,6-bisphosphatase; G6Pase, glucose-6-phosphatase.

up-regulate the expression of cell cycle protein D1 (cyclin D1) (Fu H. et al., 2018). In lung cancer, ALDOA stabilizes HIF-1 α to activate its downstream target MMP9, which enhances lung cancer invasion and migration (Chang et al., 2017). ALDOA also interacts with γ -actin to promote metastasis of non-small cell lung cancer (NSCLC) and blocking this

interaction decreases metastasis (Figure 1) (Chang et al., 2019).

Unlike ALDOA, ALDOB is significantly reduced in metastasis-inclined HCC (MIH) and its role in tumorigenesis is ambiguous (Tao et al., 2015). Overexpression of ALDOB inhibits the metastasis of liver cancer cells by inducing Ten-Eleven



Translocation 1 (TET1) (Tao et al., 2015). However, another study found that ALDOB is significantly up-regulated by GATA6 in metastatic liver cancer cell HCT116 to accelerate fructose metabolism, which is beneficial to tumor cell proliferation and metastasis (Li et al., 2017). Further efforts are required to elucidate the precise function of ALDOB in tumorigenesis.

Glyceraldehyde-3-Phosphate Dehydrogenase

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyzes the reversible conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate. Although GAPDH is a known glycolytic enzyme, it has some non-metabolic functions in tumorigenesis. GAPDH has been reported to increase glycolysis and autophagy to protect cells from caspase-independent cell death (CICD) (Colell et al., 2007). GAPDH accelerates glycolysis to increase ATP production, which is associated with its protective effect from apoptosis in the absence of caspase activation (Colell et al., 2007). Under the same conditions, GAPDH facilitates

the expression of Atg12 and increases the autophagic flow, which further preserves cell survival (Colell et al., 2007). Under starvation conditions, GAPDH can inhibit multiple transport pathways including Coat Protein I (COPI) transport by targeting the GTPase-activating protein (GAP) against ADP-Ribosylation Factor 1 (ARF1) (Yang et al., 2018). Consequently, GAPDH reduces energy consumption and maintains energy homeostasis (Yang et al., 2018).

The biological function of GAPDH is closely related to its subcellular location (Tristan et al., 2011). When GAPDH is localized in the cytoplasm, GAPDH can interact with the GTPase Rheb to regulate mTOR and autophagy. During glucose starvation, the interaction between GAPDH and Rheb is enhanced, which dissociates Rheb from mTORC1 to reduce its activity and induce autophagy (Lee et al., 2009). Under high glucose conditions, the glycolytic metabolite glyceraldehyde-3-phosphate interferes with the interaction between GAPDH and Rheb, which promotes mTORC1 activity (Lee et al., 2009).

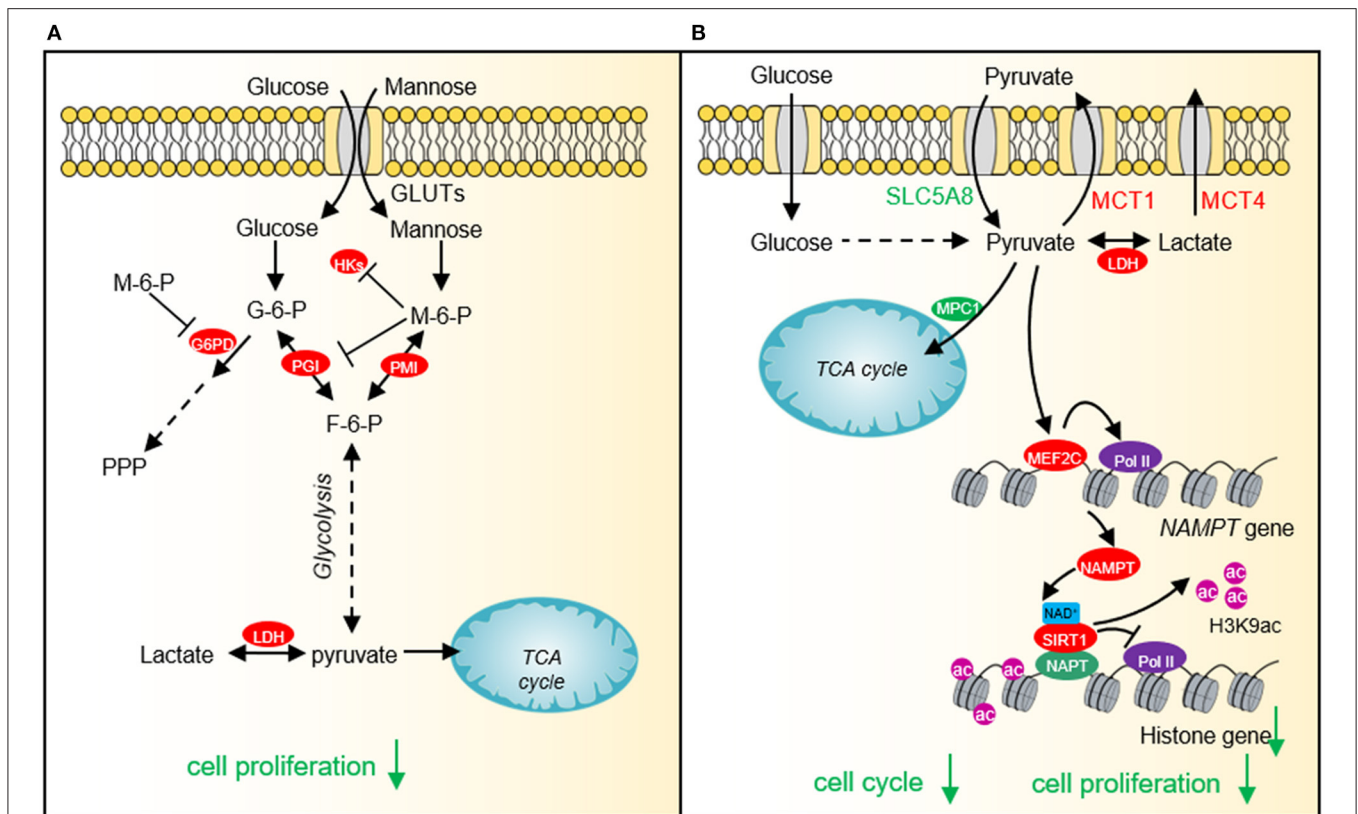


FIGURE 3 | The effect of mannose and pyruvate on cancer cell proliferation. **(A)** Exogenous mannose generates mannose-6-phosphate under the catalysis of hexokinase. High levels of mannose-6-phosphate significantly inhibit aerobic glycolysis and pentose phosphate pathway (PPP) by inhibiting the activities of hexokinase, PGI and G6PD, which affects lactate production and TCA cycle, resulting in cell growth arrest and chemotherapeutic sensitivity. **(B)** Pyruvate represses histone gene expression by inducing the expression of NAD⁺ biosynthesis enzyme, nicotinamide phosphoribosyltransferase (NAMPT) via myocyte enhancer factor 2C (MEF2C), which then increases NAD⁺ levels and activates the histone deacetylase activity of SIRT1. Downregulated histone gene expression leads to cell cycle arrest and tumor cell growth defects. Hks, hexokinases; G-6-P, glucose-6-phosphate; M-6-P, Mannose-6-phosphate; PMI, Mannose-6-phosphate isomerase; PGI, phosphoglucose isomerase; F-6-P, fructose-6-phosphate; LDH, lactate dehydrogenase; SLC5A8, Sodium-coupled monocarboxylate transporter 1; MCT1, Monocarboxylate transporter 1; MCT4, Monocarboxylate transporter 4; MEF2C, myocyte enhancer factor 2C; NAMPT, nicotinamide phosphoribosyltransferase; SIRT1, Silent mating type information regulation 2 homolog-1; NPAT, Nuclear protein of the ataxia telangiectasia mutated locus.

When GAPDH is localized in the mitochondria, GAPDH binds to voltage-dependent anion channels (VDAC) to promote the release of cytochrome *c* and apoptosis-inducing factor (AIF) to induce apoptosis under stress conditions (Tristan et al., 2011). GAPDH has also been reported to translocate into the nucleus when it is S-nitrosated (Kornberg et al., 2010). In the nucleus, GAPDH can interact with the E3 ubiquitin ligase Siah and enhance its activity, leading to Siah-dependent degradation of nuclear proteins and cell death (Hara et al., 2005). The nucleus nitrosylated GAPDH can also interact with the histone deacetylase SIRT1, HDAC2, and DNA-activated protein kinase (DNA-PK) to inhibit their catalytic activity (Kornberg et al., 2010).

GAPDH undergoes various types of covalent modifications, which regulate its localization and/or activity. GAPDH has been reported to be phosphorylated at serine 122 (S122) by AMP-activated protein kinase (AMPK), which promotes its localization in the nucleus (Chang et al., 2015). In the nucleus, the AMPK-phosphorylated GAPDH can competitively bind to SIRT1 and

displace SIRT1 repressor DBC1 to activate SIRT1 (Chang et al., 2015). As SIRT1 can stimulate autophagy by deacetylating autophagy protein LC3, the nucleus GAPDH increases autophagy to facilitate cell survival in the absence of glucose (Chang et al., 2015). In addition, GAPDH can be acetylated by histone acetyltransferase p300 and CREB-binding protein CBP, which then enhances the catalytic activity of p300/CBP in a positive feedback manner (Figure 1) (Sen et al., 2008). The nitrosylated GAPDH is translocated to the nucleus and interacts with p300/CBP. Upon acetylation, the nitrosylated GAPDH can deliver the N-Nitroso group to p300/CBP to promote their self-acetylation and enhance their activity (Sen et al., 2008). Activated p300/CBP up-regulates the transcription of their downstream targets, i.e., P53 to inhibit tumor cell proliferation (Tristan et al., 2011).

Pyruvate Kinase

Pyruvate kinase (PK) is the last rate limiting enzyme in glycolysis, which catalyzes the production of pyruvate from

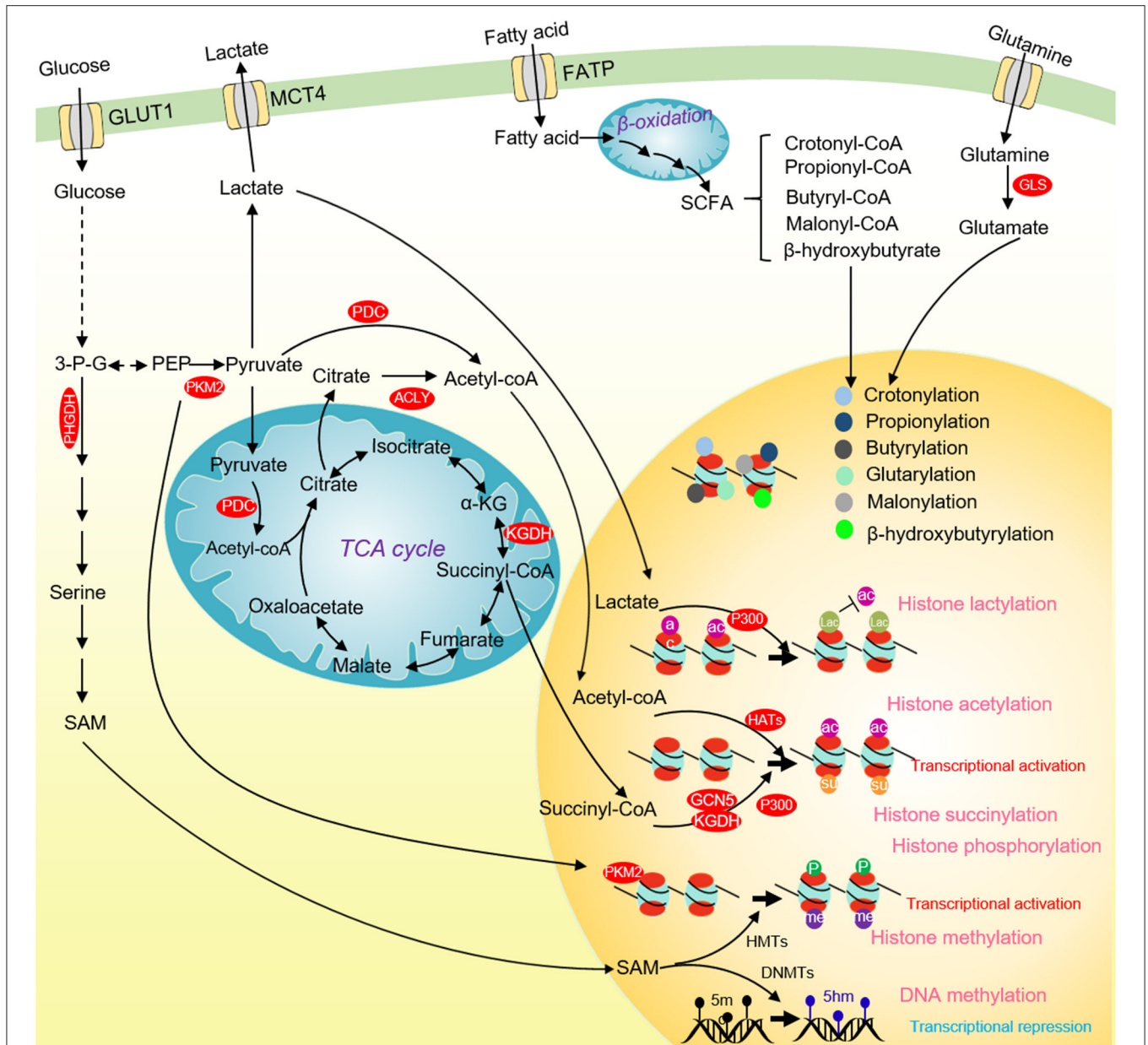


FIGURE 4 | Glucose metabolism and chromatin modifications in cancer cells. ACLY and PDC contribute to nuclear acetyl-CoA production and subsequent histone acetylation and gene activation. Glucose-derived serine and one-carbon metabolism are accelerated in cancer cells to produce SAM. SAM not only enhances DNA methylation to repress the transcription of tumor suppressor genes, but also activates the transcription of tumor-promoting genes by methylating histones. Nuclear PKM2 phosphorylates STAT3 to activate CCND1 transcription and promote cell cycle progression. The TCA cycle intermediate succinate-CoA is fueled to histone succinylation by succinyltransferase (α -KGDH, GCN5, and p300) to activate gene transcription. p300 uses lactate as a substrate to catalyze the lactylation of multiple histone lysine residues to inhibit histone acetylation. Some short-chain fatty acids produced by β -oxidation of fatty acids can provide substrates for histone crotonylation, propionylation, butyrylation, β -hydroxyisobutyrylation, glutarylation and malonylation. ACLY, ATP-citrate lyase; PKM2, pyruvate kinase M2; α -KG, α -ketoglutarate; SCFAs, short-chain fatty acids; 3-P-G, 3-phosphoglycerate; SAM, S-adenosyl methionine; HMTs, Histone methyltransferases; DNMTs, DNA methyltransferases; GCN5, general control non-derepressible 5; p300, histone acetyltransferase p300.

phosphoenolpyruvate (PEP). PK has four different subtypes L, R, M1, M2 that are encoded by two different genes *PKLR* and *PKM*. The L-type and R-type isozymes are encoded by the gene *PKLR* with differential splicing of RNA. While L-type isoenzyme is mainly expressed in liver, kidney, and intestine,

R-type isoenzyme is mainly expressed in erythrocytes (Mazurek, 2011). *PKM* gene can undergo alternative splicing to form PKM1 containing exon 9 or PKM2 containing of exon 10. Although PKM1 can activate glucose catabolism, stimulate autophagy, and promote the proliferation of malignant tumors, including

pulmonary neuroendocrine tumors (NETs) and small cell lung cancer (SCLC) (Morita et al., 2018), PKM2 is considered as a specific pyruvate kinase in tumor cells (Israelsen and Vander Heiden, 2015; Morita et al., 2018). PKM2 exists in two states: a dimeric form and a tetrameric form with different PK activities. When PKM2 is in a tetrameric state, it has high PK activity to participate in glycolysis; PKM2 has low PK activity in a dimeric state (Israelsen and Vander Heiden, 2015). Compared with constitutive active PKM1, the activity of PKM2 is low and activated only in the presence of allosteric activators (Chaneton and Gottlieb, 2012). The low PK activity of PKM2 contributes to the “Warburg effect” and metabolic reprogramming in cancer cells. For example, PKM2 diverts glucose metabolism to anabolic metabolism, including the pentose phosphate pathway (PPP), uronic acid pathway (UAP), and polyol pathway (PYP) in a variety of tumor cells and clinical cancer patients, which allows cells to synthesize biological macromolecules (Zhang Z. et al., 2019). The work in yeast revealed that the low PK activity facilitates the diversion of glycolysis to pentose phosphate pathway, which enables cells to accumulate NADPH to maintain the redox balance (Tosato et al., 2012). This implies an important role of PKM2 in tumorigenesis by regulating the antioxidant defense of tumor cells as the strong deregulation of the oxidative stress network has been described in yeast cells with chromosome translocation, which serves as model to study the formation of neoplastic mammalian cells (Sims et al., 2016). In fact, in human lung cancer cells, increased intracellular reactive oxygen species (ROS) concentrations inhibits the glycolytic enzyme pyruvate kinase M2 (PKM2) by oxidating PKM2 at Cys358, which is required to divert glucose flux into the pentose phosphate pathway to combat ROS (Anastasiou et al., 2011).

Due to its important role in tumorigenesis, PKM2 is regulated at both transcriptional and post-transcriptional levels. Three splicing factors, hnRNPL (PTB), hnRNPAI, hnRNPA2 can directly bind exon 9 of PKM mRNA, which releases exon 10 and promotes PKM2 expression (Chen et al., 2012). Once activated by epidermal cell growth factor (EGF), the epidermal cell growth factor receptor (EGFR) upregulates the expression of PKM2 by activating the PLC γ 1-PKC ϵ -IKK β -RelA signaling cascade (Yang et al., 2011). PKM2 also undergoes some posttranslational modifications to regulate its activity (Zhang Z. et al., 2019). The acetylation of PKM2 at lysine 305 (K305) reduces its kinase activity by reducing its binding affinity to PEP (Lv et al., 2011). Meanwhile, the acetylation of PKM2 at K305 increases its interaction with heat shock cognate protein 70 (HSC70), which then promotes its degradation by chaperone-mediated autophagy (Lv et al., 2011). The acetylation of PKM2 at lysine 433 (K433) inhibits its PK activity by interfering with its binding to allosteric activator FBP (Lv et al., 2013). PKM2 is phosphorylated by fibroblast growth factor receptor type 1 (FGFR1) at tyrosine 105 (Y105), which inhibits its binding to FBP, resulting in a decrease of its activity (Hitosugi et al., 2009).

PKM2 has been reported to function as a transcription cofactor to regulate gene expression. PKM2 can directly interact with the HIF-1 α and facilitate the recruitment of HIF-1 α and p300 to hypoxia response elements to activate the transcription of HIF-1 α target genes (Luo et al., 2011). Nuclear PKM2 binds

to β -catenin/TCF/LEF, thereby activating the expression of β -catenin downstream genes, i.e., CCND1 and MYC to promote cell proliferation (Yang et al., 2011). PKM2 forms a complex with pyruvate dehydrogenase (PDC) and p300, which promotes histone acetylation and activates the transcription of aromatic hydrocarbon receptor genes (Figure 1) (Zhang Z. et al., 2019).

Notably, PKM2 has been reported to function as a protein kinase to perform a variety of biological functions. PKM2 phosphorylates the mTORC1 inhibitor AKT1S1 to activate mTORC1 signaling pathway, inhibit autophagy in cancer cells and accelerates oncogenic growth (He et al., 2016). PKM2 inhibits oxidative stress-induced apoptosis by phosphorylating BCL2 to increase its protein stability (Liang et al., 2017). PKM2 phosphorylates the signal transducer and activator of transcription 3 (STAT3) to activate the expression of genes required for tumor cell proliferation (Li et al., 2015) (Figure 1). Nuclear PKM2 phosphorylates β -catenin at tyrosine 333 (Y333) to enhance β -catenin recruitment and dissociate histone deacetylase HDAC3 at the CCND1 promoter region, which eventually promotes CCND1 transcription and cell cycle progress (Yang et al., 2011). PKM2 has also been reported to modulate histone modifications, which will be discussed later.

Lactate Dehydrogenase

The LDH family has three isoenzymes: LDHA, LDHB, and LDHC. Among them, LDHA catalyzes the conversion of pyruvate to lactate (Feng et al., 2018); LDHB catalyzes the conversion of lactate to pyruvate (Brisson et al., 2016); LDHC is only expressed in the testis (Hua et al., 2017). LDHA is highly expressed in a variety of tumor cells, includes hepatocellular carcinoma, breast cancer, pancreatic cancer, sophageal squamous cell carcinoma (Sheng et al., 2012; Zhao et al., 2013; Hua et al., 2017; Mohammad et al., 2019; Zhou et al., 2019). Knockout or inhibition of LDHA significantly retards tumor cell proliferation, metastasis, and induces cell apoptosis (Zhuang et al., 2010; Miao et al., 2013), indicating that LDHA plays an important role in tumorigenesis and metastasis.

Under both normal and hypoxic conditions, tumor cells rely heavily on LDHA for energy production (Fantin et al., 2006). LDHA may increase the carcinogenicity of intestinal-type gastric cancer (ITGC) by indirectly regulating the expression of octamer-binding transcription factor 4 (Oct-4) (Zhang et al., 2012). LDHA also protects tumor cells from ROS and apoptosis (Le et al., 2010).

The activity of LDHA can be regulated by post-translational modifications. LDHA is phosphorylated at tyrosine 10 (Y10) by oncogenic receptor tyrosine kinase FGFR1, which facilitates the formation of active LDHA tetramers (Fan et al., 2011). FGFR1-catalyzed LDHA phosphorylation can be enhanced by adenylate kinase hCINAP to augment the catalytic activity of LDHA (Ji et al., 2017). LDHA can also be acetylated and recognized by HSC70, which then delivers LDHA to lysosome to be degraded (Zhao et al., 2013).

LDHB is also essential for tumorigenesis and tumor cell survival, which is associated with its regulatory role in autophagy. Protons generated by LDHB is necessary to promote lysosomal acidification and maintain basal autophagy in cancer cells (Brisson et al., 2016). LDHB can be phosphorylated by Aurora-A

to promote glycolysis and tumor progression (Cheng et al., 2019). In addition, LDHB is acetylated at lysine 329 (K329), which can be deacetylated by SIRT5 to enhance its activity (Shi et al., 2019). SIRT5-mediated LDHB deacetylation promotes autophagy and tumorigenesis (Shi et al., 2019).

Gluconeogenesis Enzymes and Tumorigenesis

The glucose concentration in the central area of solid tumors is low (Butler et al., 1975). In the absence of glucose, tumor cells need to use smaller carbon substrates such as lactate and amino acids to synthesize glucose and precursors required for tumor cell growth by gluconeogenesis (Hu et al., 2017). Therefore, the key enzymes in the process of gluconeogenesis are also critical to cancer occurrence and development.

Pyruvate Carboxylase

Pyruvate carboxylase (PC) not only provides oxaloacetate for gluconeogenesis, but also participates in the *de novo* synthesis of fatty acids and the synthesis of glycerol (Jitrapakdee et al., 2006). PC catalyzes the conversion of pyruvate to oxaloacetate, which is then condensed with acetyl-CoA to form citrate. The PC-mediated pyruvate/citrate cycle is necessary for *de novo* fatty acid synthesis (Ballard and Hanson, 1967; Kajimoto et al., 2005). Glycerol is also derived from oxaloacetate with the coordinated action of PC and phosphoenolpyruvate carboxykinase (PEPCK). PEPCK converts oxaloacetate to phosphoenolpyruvate (PEP), which is subsequently converted to glycerol (Reshef et al., 2003).

PC is overexpressed in human breast cancer tissues and correlated with the late stage of tumor progression (Phannasil et al., 2015). PC is important to support the growth and invasion of breast cancer (Phannasil et al., 2015). In addition to anaplerosis, PC affects pyruvate cycling and biosynthesis of metabolites such as the serine, glycine, 5-carbon sugar, and fatty acids (Phannasil et al., 2017).

Phosphoenolpyruvate Carboxykinase

Phosphoenolpyruvate carboxykinase (PEPCK) decarboxylates and phosphorylates oxaloacetate to form PEP in the second step of gluconeogenesis. PEPCK has two isozymes: PEPCK1 (encoded by *PCK1*), PEPCK2 (encoded by *PCK2*), which are distributed in the mitochondria and cytoplasm, respectively (**Figure 1**). PEPCK1 is overexpressed in colorectal cancer and melanoma (Li Y. et al., 2015), whereas PEPCK2 is highly expressed in lung cancer (Vincent et al., 2015), prostate cancer (Zhao et al., 2017), and breast cancer (Mendez-Lucas et al., 2014).

The effect of PEPCK on tumorigenesis is tissue-specific. Overexpression of PEPCK1 activates mTORC1 to promote glycolysis and facilitate colorectal cancer proliferation (Vincent et al., 2015). Under the conditions of glucose deficiency, amino acid limitation, and endoplasmic reticulum (ER) stress, the transcription of PEPCK2 is up-regulated, thereby increasing the adaptability of breast cancer cells to stress conditions (Morita et al., 2018). However, PEPCK1 has been reported to be down-regulated and function as a tumor suppressor in clear cell renal cell carcinoma (ccRCC), liver cancer and hepatocellular carcinoma (HCC) (Tuo et al., 2018, 2019; Shi et al., 2020).

Overexpression of PEPCK1 in liver cancer cells significantly reduces the level of cellular ATP to activate AMPK and promote the expression of p27, which causes cell cycle arrest at G1 phase (Tuo et al., 2019). Knockdown of PEPCK1 in ccRCC cells increases the stability of LDHA to enhance the “Warburg effect” and promote cell proliferation and metastasis (Shi et al., 2020). Overexpression of PCK1 can inhibit proliferation of hepatoma cells by reducing the production of ROS and repressing the expression of thioredoxin reductase 1 (TXNRD1) (Tuo et al., 2018).

Fructose-1,6-Bisphosphatase

Fructose-1,6-bisphosphatase (FBPase) catalyzes the second rate-limiting reaction of gluconeogenesis. There are two isoforms of FBPase in mammals: FBP1 (liver) and FBP2 (muscle). Both FBP1 and FBP2 function as tumor suppressors to inhibit the proliferation of tumor cells. Depletion of FBP1/2 contributes to the initiation, promotion and progression of a variety of tumors, including pancreatic ductal adenocarcinoma (PDAC) (Moore et al., 2012), ccRCC (Hirata et al., 2016), colon cancer (Zhang et al., 2016), gastric cancer (Bigl et al., 2008), lung cancer (Gutteridge et al., 2017), and cervical carcinoma (Zhang Y. P. et al., 2019). The FBP1 promoter region in tumor cells is hypermethylated to silent its expression, which is beneficial to tumor cell survival and proliferation (Gutteridge et al., 2017). Knockdown of FBP1 can promote the epithelial-mesenchymal transition, invasion, and metastasis of prostate cancer cells by activating the MAPK signaling pathway, while overexpression of FBP1 can inhibit the proliferation and metastasis of cholangiocarcinoma cells through the Wnt/ β -catenin pathway (**Figure 1**) (Zhao et al., 2018). FBP2 has also been reported to activate the AMPK signal transduction, inhibit the Akt-mTOR pathway, attenuate glucose metabolism, enhance cell apoptosis, and inhibit tumor cell proliferation (**Figure 1**) (Li et al., 2013).

Glucose-6-Phosphatase

Glucose-6-phosphatase (G6Pase) catalyzes the last step of gluconeogenesis, which consists of glucose-6-phosphatase catalytic subunit (G6PC) and glucose-6-phosphate translocase (G6PT). G6PT transports glucose-6-phosphate (G-6-P) from the cytoplasm into the endoplasmic reticulum (ER) lumen, where G-6-P is hydrolyzed by G6PC. G6Pase is overexpressed in non-gluconeogenic tumors such as ovarian cancer and glioblastoma (Wang and Dong, 2019). In G6PC-rich ovarian cancer and glioblastoma, G6PC facilitates tumor growth by promoting glycogenolysis. Knockdown of G6PC activates the expression of glycogen synthase and reduces the expression of glycogen phosphorylase, leading to accumulation of glycogen and cell cycle arrest, thereby inhibiting tumor cell proliferation and triggering cell death (Wang and Dong, 2019). In addition, G6PC positively regulates cell cycle progression by modulating cyclin dependent kinase inhibitor 1B (CDKN1B) (Guo et al., 2015). Inhibition of G6PC can enhance the phosphorylation of CDKN1B, thereby reducing the expression of CDK2 and cyclin D1, leading to cell cycle arrest (Guo et al., 2015). G6PT can also promote the invasion of glioblastoma in combined with membrane type 1 matrix metalloproteinase (MT1-MMP)

(Fortier et al., 2008). Inhibition of G6PT and MT1-MMP blocks the MAPK pathway and prevents brain tumor invasion (**Figure 1**) (Fortier et al., 2008). Under hypoxia conditions, knockout of G6PT induces necrosis of glioblastoma cells (Lord-Dufour et al., 2009). However, in glycemic-rich tissues such as liver, G6PC mainly acts on gluconeogenesis and glycogen accumulation, which is not beneficial for tumorigenesis. Thus, G6PC is often expressed at low levels in liver cancer tissues to accumulate a large amount of G-6-P, which could be used for nucleotide synthesis (Wang et al., 2012).

TCA Cycle and Tumorigenesis

TCA cycle is the central hub of energy metabolism, macromolecule synthesis, and redox balance. Enzymes in the TCA cycles play important roles in cancer metabolism and tumorigenesis (Anderson et al., 2018). In this section, we will describe the following TCA enzymes: citrate synthase (CS), isocitrate dehydrogenase (IDH), α -ketoglutarate dehydrogenase complex (α -KGDHC), and succinate dehydrogenase (SDH).

Citrate Synthase

Citrate synthase (CS) is the first rate-limiting enzyme in the TCA cycle, catalyzing the formation of citrate from acetyl-CoA and oxaloacetate (**Figure 2**). Growing evidence indicates that CS plays an important role in regulating cancer cell growth and tumorigenesis (Chen L. et al., 2014). Knockdown of CS inhibits tumor cell proliferation, cell colony formation, cell migration, cell invasion, and cell cycle progression (Cai et al., 2020).

The expression of CS is regulated by STAT3. Inhibition of STAT3 down-regulates the expression of CS and thus inhibits cell growth and proliferation (MacPherson et al., 2017). Exogenous addition of sodium citrate attenuates this inhibitory effect (MacPherson et al., 2017).

Isocitrate Dehydrogenase

Isocitrate dehydrogenase (IDH) is the second rate-limiting enzyme in the TCA cycle. IDH is composed of three isoenzymes: the cytoplasmic IDH1 and the mitochondrial IDH2/3 (**Figure 2**). IDH is mutated in a variety of tumor cells (Sajjani et al., 2017). IDH mutations stimulate the occurrence of cancer in a variety of biological processes. Tumor cells with IDH1R132H mutations can increase the level of HIF-1 α , thereby promoting tumor cell growth (**Figure 2**) (Zhao et al., 2009). The IDH1 R132H mutant catalyzes the conversion of α -KG to oncometabolite 2-hydroxyglutamate (2-HG) (**Figure 2**). The mutations of R172 and R140 in IDH2 lead to accumulation of 2-HG at extremely high levels (Dang et al., 2016). High levels of 2-HG competitively inhibit the activities of α -KG-dependent histone demethylase and TET2 DNA demethylase, leading to global chromatin methylation disorders, which is beneficial to tumorigenesis (Chowdhury et al., 2011; Xu et al., 2011). Interestingly, 2-HG has also been reported to repress tumor cell proliferation by targeting FTO/m⁶A/MYC/CEBPA signals (**Figure 2**) (Su et al., 2018). R-2HG targets Fat mass and obesity-associated (FTO) and inhibits its RNA demethylase activity, which significantly increases the abundance of m⁶A in cancer cells, leading to degradation of myc/CEBPA mRNAs in an m⁶A-dependent manner (Su et al.,

2018). As a consequence, tumor cell proliferation is impaired (Su et al., 2018). Inhibition of FTO by R-2-HG also ameliorates aerobic glycolysis by increasing m⁶A levels in the mRNA of phosphofructokinase (PFKP) and LDHB, which reduces the expression of PFKP and LDHB (Qing et al., 2021).

α -Ketoglutarate Dehydrogenase Complex

α -ketoglutarate dehydrogenase complex (α -KGDHC) is the third rate-limiting enzyme in the TCA cycle, which is composed of α -KG dehydrogenase (OGDH), dihydrolipidamide S-succinyltransferase (DLST) and dihydrolipidamide dehydrogenase (DLD). The expression of OGDH is low in many cancers due to DNA hypermethylation at its promoter and the low expression of DLD is related to the poor prognosis of some cancer patients (Zhang et al., 2015; Shin et al., 2020). Recent studies have shown that the α -KGDH complex enters into the nucleus and acts with lysine acetyltransferase 2A (KAT2A) to catalyze histone succinylation, which is beneficial for cell proliferation and tumor development (**Figure 2**) (Wang et al., 2017).

Succinate Dehydrogenase

Succinate dehydrogenase (SDH) converts succinate to fumarate. Mutations or loss of function of SDH can lead to hereditary paraganglioma, pheochromocytoma, and other genetic syndrome (Sajjani et al., 2017). The single-base substitution of SDH that causes a 33-amino acid C terminal truncation of SDHC protein, increases the intracellular ROS, which leads to metabolic stress, genome instability, and promote tumorigenesis (Slane et al., 2006). Meanwhile, SDH mutation can lead to the accumulation of succinate, which can activate succinate receptor 1 (SUCNR1), also known as regulatory G protein coupled metabolic receptor 91 (GPR91), and stimulate the release of vascular endothelial growth factor (VEGF), which then activates various kinase signal transduction pathways involved in tumorigenesis, angiogenesis, and other biological processes (Sajjani et al., 2017).

IMPACT OF GLUCOSE METABOLITES ON TUMORIGENESIS

In order to fulfill the needs of tumor cell growth and proliferation, tumor cells must increase the uptake of nutrients. Glucose and glutamine are the two main nutrients used for cell proliferation and biomacromolecule synthesis in tumor cells (Pavlova and Thompson, 2016). Lactate has recently been shown to serve as an energy source to help tumor cells survive in the absence of glucose (Rabinowitz and Enerback, 2020). Therefore, glucose-derived intermediate metabolites have become the targets of cancer treatment. Limiting the glucose uptake or repressing the expression and activity of glucose transporter GLUT1 can significantly inhibit the proliferation and survival of a variety of tumor cells (Gras et al., 2014). Mannose, as a monosaccharide, shares the same transporter with glucose, which significantly inhibits the growth of various tumor cells and the proliferation of xenogeneic tumors in nude mice (**Figure 3A**) (Gonzalez et al., 2018). 2-DG is a glucose analog, which is also transported by

GLUT into cells and then phosphorylated by hexokinase to form 2-deoxy-D-glucose-6-phosphate (2DG-6-P) (Zhang et al., 2014). The accumulation of 2DG-6-P attenuates glycolysis by non-competitively inhibiting HK and competitively inhibiting PGI, which in turn leads to reduced ATP production, cell cycle arrest, and cell death (Figure 1) (Zhang et al., 2014).

Pyruvate

Our recent study shows that cancer cells prefer low intracellular pyruvate as the intracellular pyruvate concentration is lower in cervical cancer and lung cancer than adjacent normal tissues (Ma et al., 2019). Exogenous supplied pyruvate inhibits the proliferation of various types of cancer cells, including human cervical cancer cells, liver carcinoma cells, and breast adenocarcinoma cells pyruvate as well as xenografted tumor, implying that pyruvate can function as a potential anti-cancer compound (Ma et al., 2019). Further study indicates that pyruvate reduces the expression of core histone genes to decompact chromatin structure and cause cell cycle arrest (Figure 3B) (Ma et al., 2019). Mechanistically, pyruvate induces the expression of NAD⁺ biosynthetic enzyme nicotinamide phosphoribosyl transferase (NAMPT) by activating myocyte enhancer factor 2C (MEF2C). The up-regulated NAMPT significantly promotes the biosynthesis of NAD⁺, thereby enhancing the activity of the NAD⁺-dependent histone deacetylase SIRT1. The activated SIRT1 reduces H3K9ac in the promoter region of histone genes and represses histone gene transcription (Ma et al., 2019).

The pyruvate analogs have also been reported to have anti-cancer effects. 3-bromopyruvate not only effectively attenuates aerobic glycolysis of tumor cells, but also inhibits mitochondrial oxidative phosphorylation (Fan et al., 2019; Linke et al., 2020). Ethyl pyruvate, another derivative of pyruvate, has recently been reported to inhibit tumor cell invasion, migration, and apoptosis (Liu Q. et al., 2019; Zhang T. et al., 2019). Specifically, ethyl pyruvate inhibits the growth of non-small cell lung cancer (NSCLC) by blocking the high mobility group box 1 (HMGB1)-RAGE axis and NF- κ B/STAT3 pathway (Liu Q. et al., 2019). Ethyl pyruvate down-regulates the expression of HMGB1 and RAGE, induces the accumulation of cell cycle inhibitor p27, which leads to blockage of cell cycle progression (Liu Q. et al., 2019; Zhang T. et al., 2019).

Lactate

Increased lactate production has been considered as an important marker of the “Warburg effect.” Lactate not only acts as an energy source and gluconeogenic precursor to protect cancer cells from glucose deprivation, but also functions as a signaling molecule to mediate a variety of biological processes (Hu et al., 2017; Brooks, 2020). As a shuttle molecule, lactate plays an important role in converting oxidative cells to glycolytic cells. Lactate inhibits prolylhydroxylase 2 activity and activates HIF-1 α in normoxic oxidative tumor cells. HIF-1 α then up-regulates the transcription of glycolytic enzymes, which accelerates glycolysis and promotes tumor growth (De Saedeleer et al., 2012). In addition to HIF-1 α , lactate also affects the transcription of key oncogenes (MYC, RAS, PI3KCA), transcription factors (E2F1), tumor suppressors (BRCA1, BRCA2) and genes involved in cell

cycle and proliferation (San-Millan et al., 2019). Lactate can also stabilize HIF-2 α and activate MYC to induce glutamine transporter ASCT2 and glutaminase 1 (GLS1). The high expression of GLS1 promotes the uptake and catabolism of glutamine, which is beneficial for the survival and proliferation of oxidative cancer cells (Brooks, 2020). Another important mechanism by which lactate regulates gene expression is causing lactylation of lysine residues on histones, which will be discussed later. Therefore, targeting lactate metabolism or inhibiting lactate uptake has become an effective strategy for tumor treatment (Brooks, 2020).

Citrate

Citrate has potential anti-tumor functions in different types of cancer cells, including acute monocytic leukemia (U937), breast cancer (MCF-7), pancreatic cancer (BxPC3), lung cancer (A549), Glioma (G6), neuroblastoma (Tet21N), pleural mesothelioma (MSTO-211H), gastric cancer BGC-823 and SGC-790 (Huang et al., 2020). Sodium citrate can attenuate glycolysis and cause cell cycle arrest by inhibiting the activity of PFK1 (Huang et al., 2020). Citrate can also reduce the expression of anti-apoptotic proteins B-cell lymphoma-2 (Bcl-2) and Myeloid cell leukemia-1 (Mcl-1) to trigger cell apoptosis (Chen L. et al., 2014).

METABOLIC REGULATION OF CHROMATIN MODIFICATIONS

Most chromatin modifying enzymes use metabolites as cofactors or substrates, so their activity is directly or indirectly regulated by these metabolites, such as acetyl coenzyme A (acetyl-CoA), S-adenosylmethionine (SAM). In addition, α -ketoglutarate, lactate, succinate, and some short chain fatty acids have recently been found to be involved in chromatin modifications. In this section, we will discuss the effects of glucose-derived metabolites and metabolic enzymes on chromatin modifications.

Contribution of Metabolism to Chromatin Modification in Cancer

Histone GlcNAcylation

Acetylglucosamine glycosylation (GlcNAcylation) is one of the most common protein post-translational modifications. It is an advanced glycation formed by a series of condensation, oxidation, and rearrangement of monosaccharides in the form of aldose (such as glucose and fructose) or glycolysis by-products (Dall’olio and Trinchera, 2017). GlcNAcylation can directly affect chromatin structure and gene expression by modifying histone residues or epigenetic regulatory factors (histone methyltransferases, protein kinases, and acetyltransferases) (Slawson et al., 2008; Sakabe and Hart, 2010; Dehennaut et al., 2014). Glycosylated histones H3 and H4 disrupt the assembly of nucleosomes and reduce histone acetylation, leading to disassembly of chromatin structure and deregulated gene expression (Chen et al., 2013). Breast cancer cells have a high level of histone H3 glycosylation; however, when the deglycase DJ-1 is knocked down, the overall level of histone glycosylation is significantly increased and the cell viability is

decreased (Zheng et al., 2019). This result indicates that when histones have excessive glycosylation, it greatly affects histone acetylation and ubiquitination and causes damage to tumor cells. DNA demethylase TET2 interacts with glycosyltransferase OGT and forms a complex at the transcription start site (TSS) to induce histone H2B S112 GlcNAcylation and promote gene transcription (Chen et al., 2013). In addition, multiple amino acid residues of histone demethylase EZH2 can be glycosylated by OGT to enhance its protein stability and enzymatic activity to promote tumor progression (Lo et al., 2018).

Histone Phosphorylation

The direct evidence to link glucose metabolism and histone phosphorylation is the finding that PKM2 phosphorylates H3 on threonine 11 (H3T11) (Yang et al., 2012). PKM2 interacts with β -catenin and binds at the CCND1 promoter region to phosphorylate histone H3T11, which causes the dissociation of histone deacetylase HDAC3 from chromatin and an increase of H3K9 acetylation (H3K9ac) at CCND1 promoter to activate CCND1 transcription (Figure 4) (Yang et al., 2012). Our group also showed that the yeast pyruvate kinase Pyk1 can form a complex called SESAME to phosphorylate histone H3T11 (H3pT11) to repress gene expression in response to glucose and serine availability (Li S. et al., 2015; Yu et al., 2017). We also find that SESAME phosphorylates H3T11 at telomeres to maintain the integrity of telomere heterochromatin during chronological aging (Zhang et al., 2021). H3pT11 can contribute to tumorigenesis by recruiting chromatin modifying factors. For example, H3pT11 can be bound by WDR5, a subunit of MLL complex to promote H3K4 methylation (Kim et al., 2014). In addition, the E3 ubiquitin ligase RNF8 can bind H3pT11 to mediate H3K4 ubiquitination and facilitate the expression of MYC and CCND1 (Xia et al., 2017).

Histone Acetylation

Acetyl-coenzyme A (acetyl-CoA) is an important substrate for histone acetylation. Acetyl-CoA is produced from pyruvate, citrate, and acetate by pyruvate dehydrogenase complex (PDC), ATP citrate synthase (ACLY), and acetyl-CoA synthetase short-chain family member (ACSS), respectively. Acetyl-CoA can also be generated from fatty acid β -oxidation as well as the metabolism of amino acids and ketone bodies (Sivanand et al., 2018). In cancer cells, deprivation of glucose, glutamine or pyruvate reduces the overall level of histone acetylation (McBrien et al., 2013). The glycolysis inhibitor 2-DG or knockdown of hexokinase, pyruvate dehydrogenase, and pyruvate kinase significantly reduces most histone acetylation, leading to compacted chromatin structure, repressed gene expression and reduced tumor cell proliferation (Liu et al., 2015; Yucel et al., 2019). These studies indicate that glucose metabolism can directly regulate histone acetylation.

In addition to modulating the intracellular acetyl-CoA level, glucose metabolism can affect histone acetylation by regulating the activity of histone deacetylase enzyme HDAC. The glucose-derived pyruvate can inhibit tumor cell proliferation by activating the HDAC activity of SIRT1 to reduce H3K9ac (Ma et al., 2019). The catalytic activity of class III histone deacetylases (Sirtuins)

depends on NAD⁺, a cofactor of glucose metabolism, which makes it sensitizes to NAD⁺ and glucose metabolism changes. Moreover, the activity of Sirtuins is regulated by some NAD⁺ producing enzymes. The nuclear LDH interacts with SIRT1 and enhances its activity by producing localized NAD⁺, which helps cells adapt to oxidative stress (Castonguay et al., 2014). GAPDH interacts with Sir2, the yeast homolog of SIRT1, and enhances its activity by elevating nuclear NAD⁺ (Ringel et al., 2013).

Histone Lactylation

Recent studies revealed that histones can undergo a new type of histone modification, histone lactylation (Figure 4) (Zhang et al., 2019). As a product of glucose metabolism, lactate serves as the substrate for histone lactylation, which can modify at ~28 residues on human and mouse core histones (Zhang et al., 2019). Like histone acetylation, the lactylated histones can directly promote gene transcription (Zhang et al., 2019). The discovery of histone lactylation provides a new insight into studying the role of lactate in tumorigenesis and metabolic diseases.

Chromatin Methylation

Chromatin methylation consists of three major types: DNA, RNA, and histone methylation. Chromatin methylation is catalyzed by methyltransferases using SAM as a methyl donor, which is mainly produced from glucose-derived serine metabolism (Yu et al., 2018). We and others have reported that the intracellular SAM concentration can specifically regulate the level of histone H3K4 trimethylation (H3K4me3) in both yeast and mouse embryonic stem cells (mESCs) (Figure 4) (Shyh-Chang et al., 2013; Wu et al., 2019). As a methyl donor, the intracellular SAM also regulates the global DNA methylation. The *de novo* DNA methylation by DNA methyltransferase 3a (DNMT3a) is sensitive to SAM changes, and SAM can effectively induce DNA methylation and reduce the expression of Vascular endothelial growth factor C (VEGF-C), thus inhibiting tumor growth (Nishikawa et al., 2015).

Chromatin Demethylation

It has been reported that α -ketoglutarate (α -KG) acts as a cofactor for several chromatin-modifying enzymes, including histone demethylase, Ten-eleven-translocation (TET) family of enzymes involved in DNA and RNA demethylation (Figure 2) (Tran et al., 2019). α -KG is an important metabolic intermediate produced in the TCA cycle, and is a key point linking carbon and nitrogen metabolism. Recent studies show that inhibition of glucose metabolism reduces α -KG level and inhibits the activity of the Jumonji family demethylase JMJD2B (Fu L. N. et al., 2018). JMJD2B can demethylate H3K9/K36 at autophagy associated gene (*ATG*) promoter to regulate autophagy (Fu L. N. et al., 2018). The glucose-derived α -KG maintains H3K27me3 at low levels to regulate chromatin accessibility and glioma cell survival (Chung et al., 2020). The TET proteins are α -KG-dependent dioxygenases that oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) to mediate DNA demethylation (Xiao et al., 2012). α -KG can regulate genome-wide DNA methylation and tumorigenesis by targeting TET (Xiao et al., 2012). In addition, the RNA demethylase, Fat mass

and obesity-associated protein (FTO) is also α -KG-dependent (Jia et al., 2011). Therefore, emerging researches for cancer therapy are aimed at manipulating the α -KG level.

As described earlier, α -KG can be converted to 2-HG by the IDH1/2 mutant. 2-HG is also a competitive inhibitor of multiple dioxygenases (Wang P. et al., 2015). R-2HG can inhibit the RNA demethylase activity of FTO, increase m⁶A at *MYC* and *CEBPA* mRNAs and reduce their stability, which ultimately inhibits tumor growth (Su et al., 2018). Thus, α -KG plays an important role in regulating chromatin (de)methylation by targeting the activity of chromatin demethylases. In addition, glycolysis can also indirectly inhibit the activity of histone demethylase Jhd2 by promoting H3K14ac, thus mediating a crosstalk between H3K14ac and H3K4me3 (Wu et al., 2019).

Histone Acylation

Histone acylation is an important chromatin modification for transcription regulation (Figure 4). There are various types of histone acylation, including crotonylation, 2-hydroxyisobutyrylation, butyrylation, propionylation, glutarylation, malonylation, and succinylation (Yu et al., 2018). These modifications are regulated by short-chain acyl-CoA species, which are produced during cellular metabolism. Histone acylation is associated with transcriptionally active genes and functions in a variety of physiological processes, including signal-dependent gene activation, spermatogenesis, tissue injury, and metabolic stress (Sabari et al., 2017). The histone acetyltransferase, p300 has crotonyltransferase activity and catalyzes H3K18 crotonylation depending on the intracellular crotonyl-CoA concentrations (Kollenstart et al., 2019). Chromodomain Y-like corepressor CDYL acts as a crotonyl-CoA hydratase to convert crotonyl-CoA to β -hydroxybutyryl, which negatively regulates histone crotonylation during spermatogenesis (Liu et al., 2017). Under chronic social defeat stress, CDYL is upregulated to reduce histone crotonylation and increase H3K27 trimethylation (H3K27me₃), leading to repressed transcription of neuropeptide VGF (Liu Y. et al., 2019). The class I histone deacetylases (HDACs) have been demonstrated to function as the major histone decrotonylases and are regulated by microbiota derived short chain fatty acids (Wei et al., 2017).

Histone propionylation is an active chromatin marker. Propionyl-CoA stimulates gene transcription by promoting the enrichment of H3K14 propionylation at promoters of active genes (Kebede et al., 2017). The MYST family of lysine acetyltransferases (KATs) MOF directly binds propionyl-CoA and possesses strong propionyltransferase activity both *in vitro* and *in vivo* (Han et al., 2018). Histone acetyltransferase p300 can also catalyze H3K23 propionylation and histone deacetylase SIRT2 can remove this modification in presence of NAD⁺, which mediates the crosstalk between histone acetylation and propionylation (Liu et al., 2009).

Similarly, histone butyrylation is catalyzed by p300/CBP and regulated by intracellular butyryl-CoA level (Chen et al., 2007). Histone K5 and K8 butyrylation is enriched at meiotic gene promoter and mediates spermatogenesis (Du et al., 2011).

Histone glutarylation and malonylation are recently identified histone modifications despite little is known about their biological functions. H4K91 can be glutarylated by lysine acetyltransferase 2A (KAT2A) and deglutarylated by SIRT7, which has been served as a new regulatory mechanism for chromatin dynamics (Bao et al., 2019). Malonylation of histone H2AK119 can inhibit H2A phosphorylation and influence chromosome segregation (Ishiguro et al., 2018). Histone malonylation also provides a new insight into neural tube defects (NTDs) caused by high glucose-induced diabetes (Zhang et al., 2020).

Histone β -hydroxybutyrylation is induced by ketogenesis under prolonged fasting (Xie et al., 2016). Ketone bodies including acetoacetic acid, β -hydroxybutyric acid and acetone are intermediate products of liver fatty acid oxidation during starvation, strenuous exercise and diabetes. SIRT3 acts as the de- β -hydroxybutyrylase and selectively catalyzes de- β -hydroxybutyrylation of histones due to its Zn-dependent domain (Zhang X. et al., 2019). Exogenous β -hydroxybutyrate treatment increases H3K9 β -hydroxybutyrylation and activates the expression of MMP-2 and VEGF in diabetic rats (Wu X. et al., 2020). Nevertheless, the role of β -hydroxybutyrylation in tumorigenesis and metastasis remains to be explored.

DEVELOPMENT OF ANTI-CANCER THERAPY BY TARGETING CANCER METABOLISM

Metabolic abnormalities in tumor cells also become the potential targets for the development of anti-cancer drugs. As previously mentioned, some metabolites have anti-cancer activity, including pyruvate, 2DG-6-P, mannose-6-phosphate, and citrate. Most metabolic enzymes that regulate epigenetic modifications are upregulated in tumors and some metabolic enzymes have become targets for cancer treatment (Yu and Li, 2017). There are some drugs targeting glycolysis of tumor cells in preclinical or clinical studies, such as inhibitors for glucose transporters (GLUTs): Phloretin, Fasentin, and lonidamine (LN) (Oudard et al., 2003; Palmieri et al., 2009; Dando et al., 2017), and gossypol, an inhibitor for LDH (Doherty and Cleveland, 2013). In addition, some anti-cancer drugs that target gluconeogenesis have been used in clinical trials. The inhibitor of PEPCK, 3-Mercaptopicolinic acid (MPA) induces tumor cell apoptosis by causing glucose starvation (Wang and Dong, 2019). CM-272 can reverse the Snail-mediated FBP1 expression defects under hypoxic conditions and inhibit the proliferation of hepatocellular carcinoma (HCC) (Barcena-Varela et al., 2019). Dexamethasone promotes gluconeogenesis by enhancing the expression of G6PC and PEPCK, thereby inhibiting the growth of HCC (Wang and Dong, 2019). As we understand more about the role of TCA cycle in tumorigenesis, targeting the TCA cycle to treat cancer has begun to emerge. For example, the IDH2 mutant has become a target for clinical cancer treatment and two drugs have been developed, Enasidenib (AG-221, inhibitors mutant IDH2) and AG-881 (inhibitors of mutant IDH1/2) (Yen et al., 2010). AG-221 is used as a single drug treatment of acute myelogenous

leukemia (AML) and solid tumors by reducing intracellular 2-HG (Yen et al., 2010). AG-881 is currently undergoing clinical trials for AML patients with IDH1/2 mutations (Yen et al., 2010). These drugs not only affect cancer metabolism, but also control chromatin modifications. Understanding the relationship between cancer cell metabolism and chromatin modifications not only helps elucidate the mechanism of tumorigenesis, but also facilitates the development of more efficient, accurate, and specific treatment strategies for cancer treatment.

DISCUSSION

Cancer cells have their specific metabolic pathways and epigenetic modifications that are distinct from normal cells, which contribute to the occurrence and development of tumors. Metabolic reprogram and the concurrent changes in chromatin modifications help tumor cells survive and proliferate in the nutrient-poor environment. Although there is significant progress toward understanding the relationship between cancer metabolism and chromatin modifications, there are still many problems that need to be resolved. First, we and others noticed that some metabolic enzymes and metabolites have both positive and negative effects on cell growth. We have previously reported that pyruvate can inhibit tumor growth by inhibiting histone gene expression (Ma et al., 2019). Pyruvate can also inhibit the activity of HDAC1/3 to trigger apoptosis of colon cancer cells (Thangaraju et al., 2009). However, pyruvate has also been reported to protect cancer cells from DNA damage and oxidative stress under certain circumstance (Taufenberger et al., 2019). Some metabolic enzymes regulate tumorigenesis in a tissue-dependent manner. PEPCK1 facilitates colorectal cancer proliferation (Yamaguchi et al., 2019); however, it functions as

a tumor suppressor in clear cell renal cell carcinoma (ccRCC), liver cancer and hepatocellular carcinoma (HCC) (Liu et al., 2018). Therefore, the anti-tumor drugs developed to target cancer metabolism may also have cell and/or tissue specificity. Secondly, as more metabolic enzymes and metabolites are found to be translocated into the nucleus, elucidating the functions of these metabolic enzymes and metabolites in the nucleus is important for development of anti-cancer therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

RM, YW, SL, and XY wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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