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DYSREGULATION OF METABOLIC ENZYMES IN TUMOR AND STROMAL CELLS: ROLE IN ONCOGENESIS AND THERAPEUTIC OPPORTUNITIES

Mohammad Aslam Khan[1,2,#], **Haseeb Zubair**[1,2,#], **Shashi Anand**[1,2], **Sanjeev Kumar Srivastava**[1,2], **Seema Singh**[1,2,3], **Ajay Pratap Singh**[1,2,3,*]

[1]Department of Pathology, College of Medicine, University of South Alabama, Mobile, AL 36617;

[2]Mitchell Cancer Institute, University of South Alabama, Mobile, AL 36604;

[3]Department of Biochemistry and Molecular Biology, College of Medicine, University of South Alabama, Mobile, AL 36688

Abstract

Altered cellular metabolism is a hallmark of cancer. Metabolic rewiring in cancer cells occurs due to the activation of oncogenes, inactivation of tumor suppressor genes, and/or other adaptive changes in cell signaling pathways. Furthermore, altered metabolism is also reported in tumor-corrupted stromal cells as a result of their interaction with cancer cells or due to their adaptation in the dynamic tumor microenvironment. Metabolic alterations are associated with dysregulation of metabolic enzymes and tumor-stromal metabolic crosstalk is vital for the progressive malignant journey of the tumor cells. Therefore, several therapies targeting metabolic enzymes have been evaluated and/or are being investigated in preclinical and clinical studies. In this review, we discuss some important metabolic enzymes that are altered in tumor and/or stromal cells, and focus on their role in supporting tumor growth. Moreover, we also discuss studies carried out in various cancers to target these metabolic abnormalities for therapeutic exploitation.

[*]Correspondence to: Ajay Pratap Singh, PhD, Professor and Director of Research, Department of Pathology, College of Medicine, Program Leader, Cancer Biology, Mitchell Cancer Institute, University of South Alabama, 1660 Springhill Avenue, Mobile, AL 36604, Tel: +1 251-445-9843, Fax: +1 251-460-6994, asingh@health.southalabama.edu.

Credit Author Statement

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[#]Authors contributed equally

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INTRODUCTION

The ability to generate energy and biomass is essential for a cell to sustain its growth and survival. Normal cells maintain an intricate balance of metabolic pathways and respond to internal and external cues as per the body's overall requirement. However, cancer cells, being highly proliferative and often encountering unusual environmental stresses, exhibit adaptive changes in metabolic pathways associated with dysregulation of metabolic enzymes [1, 2]. Indeed, enhanced uptake of glucose by cancer cells was recognized by Warburg about a century ago, and the basic idea of aerobic glycolysis in cancer, termed "Warburg effect" still holds true and has gained further support [1, 3]. Glycolysis is a physiological response to hypoxia in normal cells, but cancer cells tend to constitutively take up more glucose and produce lactate regardless of oxygen availability. Increased glycolytic flux provides quick energy and supplies glycolytic intermediates to secondary pathways to fulfill the metabolic and biosynthetic demands of proliferating cancer cells. This metabolic rewiring primarily takes place in response to the activation of oncogenes and/or inactivation of tumor suppressor genes that alter the expression of metabolic enzymes via transcriptional and post-transcriptional changes [1]. Further, mutations in genes encoding enzymes of key metabolic pathways are also associated with certain hereditary and sporadic forms of cancers [4, 5].

It is now well established that both tumor and tumor-corrupted normal cells (referred to as 'stromal' cells) reside within a malignant tumor [6]. Stromal cells include fibroblasts, endothelial cells, immune cells, nerve cells and in many cases microbial cells as well. Incidentally, metabolic rewiring has been observed in these cells of the tumor microenvironment beside cancer cells [7]. It is believed that metabolic changes in the stromal cells result from their functional interactions with the tumor cells and are possibly exploited by the tumor cells for their growth. Data suggest that tumor-stromal metabolic crosstalk is vital for the progressive growth of tumors. It also helps cancer cells in facing the challenges that they encounter during their malignant journey [7]. In this review, we discuss some of the important metabolic enzymes that are altered in tumor cells and stromal cells, and focus on their roles in supporting tumor growth. Moreover, we also discuss preclinical and clinical studies conducted to evaluate the therapeutic efficacy of targeting certain important metabolic enzymes in cancer.

Dysregulation of metabolic enzymes in cancer cells and functional significance

Metabolic enzymes are important nodes of biological metabolic networks that regulate the flux of metabolites as per the cellular and bodily requirements of sustaining growth and physiological homeostasis. This balance is altered in cancer cells, and accordingly, frequent alterations in their expression are reported (Figure 1). Below we discuss some of the important tumor cell-associated metabolic enzymes and their pathobiological significance.

a. Enzymes of the glycolytic pathway—Glycolysis is a universal metabolic pathway that occurs, albeit with variations, in all organisms, whether aerobic or anaerobic. The process is completed in 10 enzymatic steps, of which 3 are irreversible due to high Gibbs free energy [7]. An overexpression of glycolytic enzymes has been reported in several cancers and associated with multiple oncogenic or tumor suppressor transcription factors

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such as Myc, STAT3, NFκB, HIF1α, p53, etc. [8]. The activation of these transcription factors occurs either due to direct genetic alterations or because of the changes in their upstream signaling pathways. The major enzymes with altered expression are:

Hexokinase: Hexokinases (HK) help in the conversion of glucose to glucose-6-phosphate and have four important mammalian isozymes- HK I-IV- varying in their substrate affinity, physiological function, and subcellular localization [9]. All consist of two similar 50kDa halves, but only HK II has active functional sites in both the halves. Moreover, HK II is the most commonly upregulated hexokinase in nearly all cancer types and has normal expression in the muscle and heart [9]. HK II promoter is responsive to glucose, insulin, and glucagon and contains functional response elements in the distal and proximal regions with active binding sites for multiple oncogenic transcription factors, including NFκB, MYC, HIF-1α, STAT3 [10, 11]. While the upregulation of HK II by glucagon seems paradoxical, it benefits the cancer cells by allowing its synthesis regardless of the metabolic state of the individual. In some tumors, HK II promoter hypomethylation is also reported leading to its upregulation [12]. Interestingly, a non-canonical function of HK II in resisting mitochondria-induced apoptosis in cancer cells has also been demonstrated. AKT-mediated phosphorylation of HK II supports its binding to mitochondrial VDAC, which reduces the availability of the latter for interaction with pro-apoptotic proteins, thus disrupting the formation of mitochondrial permeability transition pore complex [13].

Glucose-6-phosphate isomerase: Glucose-6-phosphate isomerase (GPI) is overexpressed in many cancers and associated with poor prognosis [14]. It is primarily involved in the interconversion of glucose-6-phosphate to fructose-6-phosphate during glycolysis or gluconeogenesis. GPI is also secreted in extracellular spaces and referred to as the autocrine motility factor (AMF) since it promotes the migratory potential of cancer cells [14]. In breast cancer cells, GPI and HER2 interact in a positive feedback loop to promote tumor progression [15]. Additionally, GPI/AMF upregulates NF-κB and downregulates the miR-200 family to support EMT. Notably, the release of GPI is exclusively observed from the cancer cells suggesting therapeutic and biomarker opportunities.

Phosphofructokinase and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase: Phosphofructokinase-1 (PFK-1) mediates the second committed step in the glycolytic pathway. Its activity is stimulated by low ADP/AMP and fructose 2,6 bisphosphate (F2,6BP), whereas citrate, long-chain fatty acids, lactate, and ATP act as strong inhibitors in a negative feedback loop [4]. PFK-1 is significantly upregulated in cancer and promotes a glycolytic phenotype. F2,6BP is the most important allosteric activator of PFK-1 that promotes glycolytic flux even in the presence of ATP [16]. The synthesis and degradation of F2,6BP are carried out by a single enzyme, 6-phosphofructo-2-kinase/ fructose-2,6-biphosphatase 3, having both kinase and phosphatase activities. Four mammalian isoforms (PFKFB 1–4) are known, of which PFKFB3 is the most commonly upregulated. Hypoxia upregulates PFKFB3 through direct HIF-1α-mediated transcriptional activation. It also has the highest kinase/phosphatase activity ratio (740/1), leading to elevated F2,6BP levels and sustained high glycolytic rates through FBP1 activation [17].

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Phosphoglycerate kinase: Phosphoglycerate kinase (PGK1) mediates one of the only two ATP generating steps in the glycolytic pathway. It is highly expressed in cancers and considered a major positive regulator of the Warburg effect [8]. EGFR activation, mutant KRAS/B-Raf, hypoxic stress, etc., induce phosphorylation of PGK1 via activated ERK1/2. This leads to its mitochondrial translocation, where it phosphorylates pyruvate dehydrogenase kinase (PDK1). Activation of PDK1 suppresses the activity of pyruvate dehydrogenase complex (PDC). As a result, the conversion of pyruvate to Acetyl-CoA is inhibited suppressing the TCA cycle [18]. Additionally, PGK1 also regulates autophagy in cancer cells under stress conditions such as glutamine-deprivation and hypoxia. ARD1 acetylates PGK1 at Lys388 under stress conditions, which then phosphorylates Beclin at Ser30, which is an important initial step for the formation of autophagosomes [19]. We have also recently observed that IKK-epsilon, a member of IKK family of kinases, promotes pancreatic tumor growth by reprogramming glucose metabolism. Metabolic reprogramming is mediated through the altered expression of several metabolic enzymes, including PGK1, HKII, etc., via IKK-epsilon-induced stabilization of c-MYC [20].

Pyruvate kinase: Pyruvate kinase (PK) is the second ATP generating enzyme in glycolysis and has four major mammalian isoforms (PKM1, PKM2, PKL, and PKR). PKM2 is the embryonic isoform of PK that is widely expressed in cancer [21]. PKM2 expression cannot be attributed to fast-dividing cells since quiescent T cells and white adipose tissue also express PKM2. Despite reported overexpression of PKM2 in several cancers, its reduced expression and/or activity is shown to support cancer cell proliferation [22]. PKM2 activity is regulated by allosteric effectors (succinyl-5-aminoimidazole-4-carboxamide-1-ribose 5′-phosphate, fructose-1,6-bisphosphate, phenylalanine, cysteine, serine) and posttranslational modifications. In addition, its activity is affected by its oligomeric state, dimer or tetramer. The tetrameric form is active whereas dimeric form is inactive that diverts the glycolytic flux towards increased biomass production by blocking phosphoenolpyruvate utilization. It is also reported that the inactive dimeric PKM2 translocates into the nucleus and supports tumor cell proliferation by transcriptionally activating the expression of oncogenes [23]. Cancer cells withstand oxidative stress by promoting ROS-mediated inhibition of the tetrameric form of PKM2 that activates the pentose phosphate pathway and generates reducing cellular environment [24]. Substrate (phosphoenolpyruvate) binding affinity of PKM2 is reduced upon phosphorylation by PP60v-src-tyrosine kinase, which leads to the accumulation of different glycolytic intermediates/phosphometabolites [25]. PKM2 transfers phosphate groups directly from phosphoenolpyruvate to serine, threonine, or tyrosine residues of recipient proteins, and its important substrates include H3 histone and STAT3 among others [26].

Lactate dehydrogenase: Lactate dehydrogenase (LDHA) is an important determinant of glycolytic ability and multiple mechanisms have been attributed to its upregulated expression in cancer cells. For example, the *LDHA* promoter contains DNA-binding elements for different oncogenic transcription factors, including c-MYC, HIF-1α, CREB, AP-1, STAT3, which mediate its transcriptional upregulation [27]. In our recent studies, we observed that MYB, an oncogenic transcription factor, also positively regulated the expression of *LDHA* along with *GLUT1* in pancreatic cancer cells [28]. This is signficant

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considering our earlier findings on MYB that demonstrated its role in pancreatic tumor growth, metastasis, and desmoplasia [29, 30]. In addition, *LDHA* is also a target of several tumor suppressor miRNAs [31–33]. Direct repression of *LDHA* by miR-34a enhances the sensitivity of advanced colon cancer cells to 5-fluorouracil [31]. *LDHA* silencing also reduces the survival of cancer cells under both normoxia and hypoxia due to a decrease in ATP levels. The release of lactate from the cancer cells benefits the cancer cells by inducing an immunosuppressive microenvironment [34]. Acidic environment caused by released lactate downregulates nuclear factor of activated T cells (NFAT), which then causes an upregulation of IFN-γ transcripts in competent immune cells ($CD8^+$T and NK cell) [34]. Lactic acid produced by tumor cells also activates IL-23 expression both at transcriptional and protein levels in infiltrated immune cells. This, in turn, promotes tumor growth, metastasis and further dampens the immune surveillance by recruiting immune-suppressive M2-like macrophages and neutrophils [35, 36].

b. Enzymes of the tricarboxylic acid cycle—The tricarboxylic acid (TCA) or the Kreb's cycle operates in the mitochondrial matrix and is a central route for oxidative phosphorylation. Earlier, it was thought that the cancer cells bypass the TCA cycle entirely and operate only on the aerobic glycolytic pathway [37]. However, it is now clear that the TCA cycle not only contributes to energy production in cancer cells but also supports tumorigenesis. Moreover, the substrates of the TCA cycle also promote non-metabolic signaling involved in cancer progression. Major dysregulated enzymes in the TCA pathway are discussed below.

Pyruvate dehydrogenase complex/Pyruvate dehydrogenase kinase: The pyruvate dehydrogenase (PDH) is comprised of three components, E1-E3. E1 contains thiamine pyrophosphate (TPP), which forms a carbanion and decarboxylates pyruvate [38]. PDH, in fact, bridges the glycolysis to the TCA cycle by facilitating the generation of acetyl CoA from pyruvate. High ATP-ADP ratio and elevated Acetyl CoA activate pyruvate dehydrogenase kinase (PDK), which phosphorylates and inhibits PDH at E1. In contrast, high ADP-ATP ratio and elevated pyruvate inhibit PDK and promote PDH activity [38]. Thus, PDK acts as a gatekeeper of altered glucose metabolism in cancer. The PDK family consists of 4 highly homologous members that phosphorylate 3 sites (Ser293, Ser300, and Ser 232) on E1-alpha of PDH. PDK overexpression is observed in several tumors and associated with chemoresistance, invasiveness, and metastasis [39]. It promotes tumor cell proliferation through the conservation of pyruvate for recycling of NAD^+ via lactate dehydrogenase, production of Krebs cycle intermediates, and transamination through alanine aminotransferase [40]. Inhibition of PDKs is reported to increase PDH complex activity, mitochondrial activity, and production of reactive oxygen species (ROS) that slows tumor growth and promotes apoptosis [41]. Acetylation of PDH at Lys321 by acetyl-CoA acetyltransferase 1 (ACAT1) also leads to its inactivation via recruitment of PDK to its phosphorylation sites [42]. Deacetylation of that same lysine is catalyzed by SIRT3, and accordingly SIRT3 downregulation or ACAT1 upregulation is reported to enhance tumor growth [42]. Upregulation of HIF1α activates PDK transcriptionally, which inactivates PDH and allows increased recycling of NAD^+ via lactate dehydrogenase under hypoxic or

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pseudohypoxic conditions [43]. PDK4 is paradoxically downregulated in hepatocellular carcinoma and lung cancer and suggested to have tumor suppressor functions [44, 45].

Isocitrate Dehydrogenase: Isocitrate dehydrogenase (IDH) catalyzes the oxidation of isocitrate to alpha-ketoglutarate via a 2-step process that involves i) reduction of NAD^+/$NADP^+$ to NADH/NADPH to oxidize isocitrate to oxalosuccinate, and ii) decarboxylation of oxalosuccinate to alpha-ketoglutarate. IDH consists of 3 isozymes, IDH1-IDH3, of which the only IDH3 is found in the mitochondrial matrix [46]. Additionally, IDH3 uses NAD^+ to oxidize isocitrate, while the other two use $NADP^+$ [46]. Somatic mutations in IDH1 at R132 and in IDH2 at R172 and R140 result in a gain of new function *i.e.* catalyzing the conversion of alpha-ketoglutarate (α-KG) to D-2-hydroxyglutarate (D-2HG), which facilitates tumor proliferation [46, 47]. Mutant IDH1 also forms heterodimers with the wild-type IDH1 and inhibits its activity [48]. Knockdown of wildtype IDH1 in a glioma cell line resulted in an increased expression of HIF1α and VEGF. Similarly, forced expression of mutant IDH1 also inhibited wild type IDH1 by forming heterodimer and increased HIF1α [48]. These findings suggest that conversion of α-KG to D-2HG by mutant IDH weakens HIF1α degradation to promote tumorigenesis.

Succinate dehydrogenase: The succinate dehydrogenase (SDH) complex proteins are encoded by four nuclear genes, *SDHA, SDHB, SDHC, and SDHD,* and their folding and assembly occur in mitochondria [49]. Tumor cells display aberrant promoter hypermethylation of *SDH* genes, and their expression is also repressed by certain oncogenic miRNAs (miR-210, miR-378, and miR-31) overexpressed in response to therapy, hypoxia and other stress conditions [49–51]. SDH complex proteins are also regulated in cancer through multiple post-translational modifications [49]. Mutations in any one of the subunits can disrupt the complex formation causing a loss of function. Additionally, mutations in SDHAF2/SDH5, an SDH complex assembly factor, also result in loss of function [52]. Diminished SDH expression or activity promotes a pseudohypoxic phenotype in cancer cells due to the accumulation of succinate, which inactivates prolyl hydroxylase (PHD), leading to HIF1α stabilization [53].

c. Enzymes in gluconeogenesis—Gluconeogenesis is a pathway that generates glucose from non-carbohydrate precursors, including lactate, pyruvate, glutamine, alanine, and glycerol. This process occurs in the liver, kidney, skeletal muscles and intestine to maintain blood glucose levels under fasting or after heavy exercise. Gluconeogenesis can antagonize aerobic glycolysis in cancer exclusively by three key gluconeogenesis enzymes, which are discussed below.

Phosphoenolpyruvate carboxykinase: Phosphoenolpyruvate carboxykinase (PEPCK) exists as two isoforms, a cytosolic PCK1, and another mitochondrial, PCK2, and both catalyze the conversion of oxaloacetate to phosphoenolpyruvate. PEPCK is overexpressed in colon cancer cells and associated with decreased glucose and glutamine metabolism and diminished proliferation, clonogenic survival and tumorigenicity in a mouse model [54]. PCK2 mediates glycerol phosphate synthesis to support *de novo* synthesis of glycerophospholipid and its silencing reduces colony formation under the starved condition

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and in a subcutaneous mouse model of lung cancer [55]. Tumor-repopulating cells (TRCs) of melanoma in 3D culture reprogram glucose metabolism by hijacking the PCK1 without involving gluconeogenesis, but regulating glucose side-branch metabolism [56]. PCK1 silencing in TRCs drastically reduces glycine levels (a major metabolite of serine) and retards their growth *in vitro* and *in vivo* [56]. An overexpression of PCK2 is reported in pancreatic neuroendocrine tumors (pNET), where it regulates cellular metabolism by decreasing glycolysis but increasing mitochondrial oxidative phosphorylation [19, 57].

Fructose bisphosphatase: Fructose-1,6-bisphosphatase (FBPase) is a rate-limiting enzyme that hydrolyzes fructose 1,6-bisphosphate to fructose 6-phosphate and inorganic phosphate (Pi) and has two isoforms liver FBPase (FBP1) and muscle FBPase (FBP2). FBP2 is overexpressed in metastatic breast cancer cells (MBCC) and supports their survival and proliferation by promoting gluconeogenesis and glutamine oxidation [58]. Several contradictory studies suggest a tumor-suppressive role of FBP2 and FBP as well. FBP1 is downregulated in various cancers, and low FBP1 levels are associated with poor overall survival [59]. Exogenous expression of FBP1 also decreases tumor cell growth *in vitro* and mouse models of multiple cancer types [60]. Under complete nutrient replenished conditions, FBP1 inhibits glycolysis in breast cancer, pancreatic cancer, lung cancer and HCC cells [59]. Overexpression of FBP1 in renal carcinoma cells (RCC) results in enhanced proliferation and migration, and reduction of glycolysis [61] and its role in EMT has also been suggested [60].

Glucose 6 phosphatase: Glucose-6-phosphatase (G6Pase, G6PC) is a key enzyme involved in gluconeogenesis and glycogenolysis. It hydrolyzes D-glucose 6-phosphate to D-glucose and orthophosphate. Overexpression of G6PC is reported in ovarian cancer and associated with poor overall survival [62]. Direct targeting of G6PC via the IL6-Stat3-miR-23a axis suppresses the gluconeogenesis in a mouse model of hepatocellular carcinoma and diminishes the serum glucose levels in tumor-bearing mice [63]. Low G6PC correlates with higher uptake of fluorodeoxyglucose (FDG) in poorly differentiated HCC as compared to that in moderately differentiated HCC, indicating a connection of G6PC with tumor-grade [64].

d. Enzymes of other cancer-promoting metabolic pathways—Apart from glucose metabolism, glutamine, and fatty acid metabolism also plays an active role in cancer cell growth and proliferation [1]. These pathways can directly contribute to the energy requirements of proliferating cells or support the generation of biomass through their integration with the glucose metabolic pathway. Further detail on the most frequently dysregulated enzymes from these pathways are below:

Glutaminase: Glutamine is the most abundant amino acid in blood circulation and acts directly or indirectly as a carbon and nitrogen source for the synthesis of nucleic acids, fatty acids, and proteins. Glutaminase converts glutamine into glutamate and ammonia, and glutamate is further utilized in the amino acid biosynthetic pathway. Alternatively, it converted to α-KG, which enters into the TCA cycle for the production of energy and biosynthetic precursors for a wide range of metabolic pathways. Glutaminase is important

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for the production of glutathione, a key scavenger of reactive oxygen species (ROS) [65]. In humans, two isoforms of glutaminase are known, kidney-type (GLS) and liver-type (LGA/GLS2), of which the former has been studied extensively for its role in cancer pathogenesis [66]. Studies are also emerging that suggest the role of GLS in the microvesicle formation in cancer cells [67]. High expression of GLS is observed in several malignancies and positively correlated with disease progression, and the study demonstrated that c-myc-mediated GLS expression induced tumor cell growth and proliferation by stimulating glutamine catabolism [68]. In contrast, GLS2 is reported to have a dual role in tumorigenesis. It is downregulated in brain tumor cells where its forced expression reduces tumor cell growth *in vitro* and *in vivo* [69]. On the other hand, increased expression of GLS2 is crucial for the growth of lung, cervical and colon cancer cells [69, 70]. This functional disparity could be due to differential regulation of their activity. In the presence of phosphate, GLS has greater enzymatic acivity due to lower *Km* for glutamine as compared to GLS2 whereas the presence of ammonia increases GLS2 activity, but inhibits GLS activity [69, 71]. Small molecule inhibitors of both GLS and GLS2 have been developed of which Bis-2-(5-phenylacetamido-1, 2, 4-thiadiazol-2-yl) ethyl sulfide (BPTES) and dibenzophenanthridine-968 exhibit maximum potency [65].

Fatty acid synthase: Fatty acid synthase (also referred to as FASN) is involved in lipogenesis and responsible for the production of long-chain fatty acids from acetyl-coenzyme A (CoA) and malonyl-CoA. Except for liver and adipose tissue, all the normal cells have low FASN expression and activity, whereas it is overexpressed in multiple cancer types [72]. A gene copy gain of *FASN* in prostate adenocarcinoma along with elevated protein levels has been demonstrated by FISH and IHC analyses [73]. Ubiquitin-specific protease 2a (USP2a), an androgen-regulated enzyme overexpressed in prostate cancer, promotes the expression of FASN to support cell survival [74]. FASN silencing or pharmacological inhibition is shown to suppress the tumor growth via apoptosis induction and increased survival of breast and prostate tumor-bearing mice [75, 76].

Metabolic reprogramming in stromal cells and associated mechanisms

Stromal cells are a pool of non-malignant, heterogeneous cell types residing in the tumor microenvironment (TME). They support tumor progression, metastasis, and therapy resistance via intercellular interactions with each other and the tumor cells. Like tumor cells, they also live in a continuously changing TME and thus make adaptive metabolic changes to survive. However, their adaptive metabolic reprogramming largely depends on either the tumor-derived factors (cytokines, growth factors, extracellular vesicles, etc.) or altered metabolic composition of the TME [77] (Figure 2). Below we describe changes in bioenergetics and associated mechanisms for three important stromal cell types.

Fibroblasts: Fibroblasts have unique phenotypic plasticity. Cancer-associated fibroblasts (CAFs) acquire myofibroblasts-like phenotypic characteristics and are the most abundant component of TME. They are also a significant source of extracellular matrix (ECM) proteins. They undergo metabolic reprogramming, from oxidative phosphorylation to aerobic glycolysis, to support their proliferative growth [77]. It is shown that breast cancer cells induce oxidative stress in fibroblasts by secreting hydrogen peroxide, which inhibits

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their mitochondrial activity and increases glycolysis. This metabolic change also generates high energy intermediates like lactate and pyruvate, which are taken up by the breast cancer cells to meet their high energy demand [78]. Breast cancer cells express high levels of integrin beta 4 (ITB4), which is packed into exosomes and transferred to the stromal cells (CAFs). This exosomal transfer induces glycolysis by causing BNIP3L-dependent mitophagy in CAFs [79]. Microvesicles derived from the oral squamous cell carcinoma are also shown to change normal fibroblasts into CAFs and induce metabolic switching to aerobic glycolysis. In return, CAFs provide high energy metabolite, lactate, to the cancer cells by monocarboxylate transporter 1 and 4 [80]. Primary and metastatic tumor cell-derived exosomes can activate quiescent fibroblasts and give rise to a functionally distinct subset of CAFs by upregulating glycogen metabolism, amino acid biosynthesis, and glycolysis [80]. Breast tumor cells increase glucose and glutamine metabolism in CAFs in an MYC-dependent manner by transferring miR-105 through exosomes. In exchange, reprogrammed CAFs produce metabolic intermediates to support tumor cell growth [81]. Similarly, in prostate cancer, metabolically reprogrammed CAFs secret high amount of lactate that is taken up by prostate cancer cells and induces SIRT/PGC-1α-dependent mitochondrial activity and prostate cancer aggressiveness [82].

Immune cells: Tumor-associated macrophages (TAMs) are the most abundant immune component of TME. Increased TAM infiltration usually correlates with poor clinical outcomes in multiple cancer types [83]. TAMs are reprogrammed macrophages that not only support tumor progression and metastasis but also cause further immune suppression. Cytokines and growth factors derived from TAMs also support tumorigenesis by promoting neoangiogenesis [83]. In addition, TAMs provide nutrient availability to the tumor cells in TME. For example, TAMs secrete a high amount of iron in TME, which is taken up by the tumor cells and induces their growth and proliferation [84]. Macrophages can polarize to M1-like (tumor-suppressive) or M2-like (tumor supportive) phenotypes depending on the extracellular stimuli [85]. Data suggest that M1 macrophages rely more on glycolysis, and glycolysis inhibition renders their tumor-suppressive activity due to reduced phagocytic ability, production of pro-inflammatory cytokines and reactive oxygen species (ROS). In contrast, M2 macrophages preferentially utilize oxidative phosphorylation for their activity [85].

Glutamine metabolism is one of the indispensable pathways for macrophage activation and immune responses, and α-ketoglutarate derivative of glutamine induces the macrophage polarization to the M2 phenotype. Another amino acid, arginine, is equally important. It is catabolized by two enzymes, inducible nitric oxide synthase (iNOS) and arginase (two isozymes, arginase I, and II). iNOS facilitates the conversion of arginine into nitric oxide (NO), while arginase hydrolyzes the arginine into ornithine and urea [85]. M1 macrophages utilize iNOS for arginine metabolism and generate reactive nitrogen species (RNS) from NO that has a microbicidal or tumoricidal function. On the contrary, tumor-supportive M2 macrophages catabolize arginine into ornithine and urea by arginase II [85].

Enzyme activity profile in normal human macrophages and TAMs from colorectal tumors have suggested different metabolic profiles among M1-like and M2-like macrophages. Further, infiltrating M2-like macrophages have reduced GAPDH activity compared to M1-

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like [86]. Adenosine, a purine ribonucleoside in TME, is involved in immune evasion by eliciting inhibitory signaling in natural killer (NK) cells through adenosine receptor (A2AR) [87]. Glycolytic melanoma cells produce a high amount of lactic acid, which potentially inhibits the activity of NK- and T-cells by downregulating the nuclear factor of activated T cells (NFAT) signaling [34]. Data also suggest that a low level of triglycerides anabolic enzyme, abhydrolase domain containing 5, in tumor-associated macrophages (TAMs) promotes tumor metastasis via NF-κB-dependent matrix metalloproteinases activation [88]. The anti-diabetic drug, metformin, rewires glucose metabolism in $CD11b^+$ myeloid cells (TAMs) and induces their repolarization to the M1 phenotype leading to the suppression of the growth of osteosarcoma cells *in vivo* [89].

Tumor endothelial cells: Endothelial cells (ECs) exhibit metabolic plasticity and preferentially adopt a glycolytic phenotype despite having high oxygen in their proximity. Glycolysis in these cells is attributed majorly to increased glucose transporter1 (GLUT1), hexokinase 2 (HK2), and phosphofructokinase 1 (PFK1). Tumor-associated endothelial cells (TECs) exhibit even more glycolysis as compared to normal ECs and glycolysis inhibition in TECs reduces their proliferation, survival, and migration [90]. Data suggest that vascular endothelial growth factor (VEGF) secreted by cancer cells can increase glycolysis in TECs by upregulating glucose transporter, GLUT-1 [91]. Other TME associated factors, including hypoxia, cytokines, and growth factors, are shown to increase the expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) in TECs that controls PFK1 activity in glycolytic pathway.

Targeting metabolic abnormalities in cancer for therapeutic exploitation

In light of the essential roles of adaptive metabolic changes in the growth of cancer, their targeting is considered a novel avenue for cancer therapy (Table 1). Some of the examples are described below:

Glucose analog, 2-deoxy-D-glucose (2-DG), inhibits glucose metabolism with high efficacy. Hexokinase phosphorylates 2-DG, which cannot be metabolized any further by the cells, leading to its intracellular accumulation and inhibition of hexokinase activity [92]. Upregulation of hexokinase II is reported during the metabolic shift from oxidative phosphorylation to glycolysis, and its inhibition is shown to sensitize the cancer cells to oxidative stress therapy [93]. 3-bromopyruvate (3BP), a brominated derivative of pyruvic acid, is structurally similar to pyruvic and lactic acid. It inhibits HK II and possesses alkylating properties towards biomacromolecules [88, 93]. Moreover, 3BP also targets other glycolytic enzymes such as glyceraldehyde 3-phosphate dehydrogenase, lactate dehydrogenase, pyruvate carboxylase, and pyruvate dehydrogenase [94]. The ATP depleting effect of 3BP has been promising for the treatment of several cancers, and in some cases, it restored chemo-sensitivity [94]. Lonidamine (LND), a derivative of indazole-3 carboxylic acid, has been used to inhibit aerobic glycolysis in cancer cells. LND inhibits the HK II and other enzymes of pentose shunt- and glycolytic-pathways, possibly via cytosolic acidification. Moreover, it is also shown to inhibit mitochondrial respiration by abolishing the pyruvate import via mitochondrial pyruvate carrier, and mitochondrial electron transport complex II or complex I or both in case of ubiquinone reduction [95]. Due to its ability to

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inhibit the energy metabolism, LND, in combination with other anti-cancer agents, has been tested for the treatment of glioblastoma multiforme, breast cancer, lung, and ovarian cancers and is currently in a clinical trial [95].

A study has suggested that PFK-1 activity is regulated through allosteric inhibition by ATP and citrate. Small-molecule inhibitor, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO), indirectly targets PFK-1 by inhibiting its allosteric activator, 6-phosphofructose-2-kinase, and thus reduces glucose metabolism and synthesis of the ATP, NAD^+, NADH, and fructose 2,6 bisphosphate. 3-PO has been shown to diminish the growth of many human malignant hematopoietic and adenocarcinoma cell lines *in vitro* and *in vivo* [96–98].

Among the four isozymes, PKM2 is considered vital due to its elevated expression in cancer [21]. The knockdown of PKM2 sensitizes pancreatic cancer cells to gemcitabine therapy and colorectal cancer cells to oxaliplatin treatment [99, 100]. Tanshione IIA, a natural compound isolated from Chinese herb *Salvia miltiorrhiza*, inhibits human esophageal cancer cell growth via miR-122-mediated downregulation of PKM2 [101]. Moreover, Shikonin, alkannin, and their structural analogs also inhibit the activity of PKM2 and reduce cancer cell proliferation and survival. In a clinical trial, shikonin mixture reduced the tumor size (25% in diameter) and increased the survival rate (36.9%) in lung cancer patients [102].

Another study has suggested that CPI-613, a lipoid analog, strongly disrupts the mitochondrial metabolism by phosphorylating pyruvate dehydrogenase (PDH). It also targets alpha-ketoglutarate dehydrogenase through redox modification [103]. Dichloroacetate (DCA) inhibits the pyruvate dehydrogenase kinase (PDK) and decreases the glycolytic flux towards the lactate; however, the clinical trial data suggest that it is effective in some cancers only. 2-chloroproprtionate, an allosteric inhibitor of PDK, also works similar to DCA [104]. Gossypol, a polyphenolic binaphthyl disesquiterpene compound, targets lactate dehydrogenase by competitively inhibiting the interconversion of NADH and NAD^+ [105]. A small-molecule inhibitor, FX11, inhibits LDH-A-dependent tumor growth by reducing ATP levels and increasing oxidative stress. Quinoline 3-sulphonamide also exerts LDH inhibitory activity and impairs survival in numerous cancer cell lines [106]. Oxamic acid, a structural isostere of pyruvic acid, inhibits the LDH activity, and induces ROS in cancer cell lines [88]. Additionally, inhibition of HIF-1α could be a practical approach to reduce tumor growth by altering glucose metabolism. For example, FDA-approved drug (Topotecan) for the treatment of ovarian cancer, inhibits HIF-1α leading to a reduced expression of GLUT-1 in patients with advanced solid cancers [107].

Pharmacological inhibition of gluconeogenesis enzyme, PEPCK (PEPCKi), reduces phosphoenolpyruvate (PEP) in colon cancer cells leading to an increase in PEPCK substrate, oxaloacetate, and growth inhibition [108]. Another PEPCK inhibitor, 3-mercaptopicolinic, induces apoptosis in lung cancer cells by depleting glucose. Interestingly, dexamethasone treatment induces gluconeogenesis by upregulating PEPCK in low PEPCK-expressing hepatocellular carcinoma cells and inhibits their growth and angiogenesis. Forced expression of PEPCK1 in T cells induces metabolic reprogramming bolstering their tumoricidal activity and thus increasing the survival of tumor-bearing mice [88]. HDAC inhibitors (sodium butyrate, vorinostat, and panobinostat) upregulate FBP1 expression and inhibit glycolysis in

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multiple cancers [59]. In another report, FBP1-derived small peptide inhibitor, FBP1-E4, is shown to enhance gemcitabine toxicity in pancreatic tumor cells [59]. Competitive inhibitor of G6PT (catalytic subunit of G6PC), chlorogenic acid, inhibits migration of glioblastoma cells by blocking matrix metalloproteinase (MMP)-2 secretion. Human brain tumor-initiating cells (BTIC) require G6PC to counteract the effect of 2-DG, and its silencing reduces their survival and malignant potential under glycolysis inhibited condition [109].

Since tumor and stromal cells, especially immune cells, have overlapping metabolic needs, targeting of metabolic reprogramming for effective anti-tumor therapies should be very specific. For example, 2-DG inhibits tumor growth by inhibiting glycolysis, but it has an unwanted effect on T cell metabolism. Although in another case, inhibition of lactic acid secretion by lenalidomide reduces tumor growth and enhances T cell activation. In colorectal cancer, inhibition of lactate production is shown to reduce tumor cell growth and improve the therapeutic response of 5-fluorouracil [47].

CONCLUSION AND FUTURE PERSPECTIVES

Metabolic adaptation of tumor and stromal cells via altered expression of metabolic enzymes is now well established. It is also proven that metabolic reprogramming plays an essential role in cancer development. Altered metabolism not only helps cancer cells survive and grow but confers resistance to therapeutic interventions as well. Identifying the dependence of tumor cells on certain metabolic enzymes in preclinical and clinical studies has opened up new avenues for therapy development or the improvement of existing therapies. However, there are challenges along the way. Certain available drugs that can target cancer metabolism may not be clinically useful due to their lack of specificity and broad effects on multiple cell types. In some instances, metabolic alterations appear to play contrasting roles in different cancers, suggesting their context-dependent actions. Thus, efforts are required to improve understanding of associated mechanisms in parallel investigations. Regardless, existing data and current thrust in cancer metabolic research give us hope that novel therapies will soon emerge to provide additional options to oncologists to better manage lethal malignancies.

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ABBREVIATIONS:

LDH	Lactate dehydrogenase
HK	Hexokinase
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
EGFR	Epidermal growth factor receptor
NFκB	Nuclear factor kappa light chain enhancer of activated B cells

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STAT3	Signal transducer and activator of transcription 3
TCA	Tricarboxylic acid cycle
CAFs	Cancer-associated fibroblasts
TAMs	Tumor-associated macrophages
2-DG	2-deoxy-D-glucose
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
TME	Tumor microenvironment
HIF1α	Hypoxia-inducible factor 1-alpha
PDC	Pyruvate dehydrogenase complex

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Highlights:

- To maintain a proliferative state and survive under hostile environments, cancer cells make adaptive changes in cellular metabolism.
- Transformed cellular metabolism is associated with dysregulation of metabolic enzymes.
- High metabolic demand of cancer cells affects the tumor microenvironment due to unusual uptake of certain nutrients and release of metabolic derivatives and associated factors in the extracellular milieu.
- Metabolic rewiring is also observed in stromal cells likely resulting from their adaptation to the remodeled tumor microenvironment and facilitated by tumor-derived factors.
- Tumor-stromal metabolic crosstalk is vital for progressive growth of tumors providing opportunities for therapeutic exploitation.

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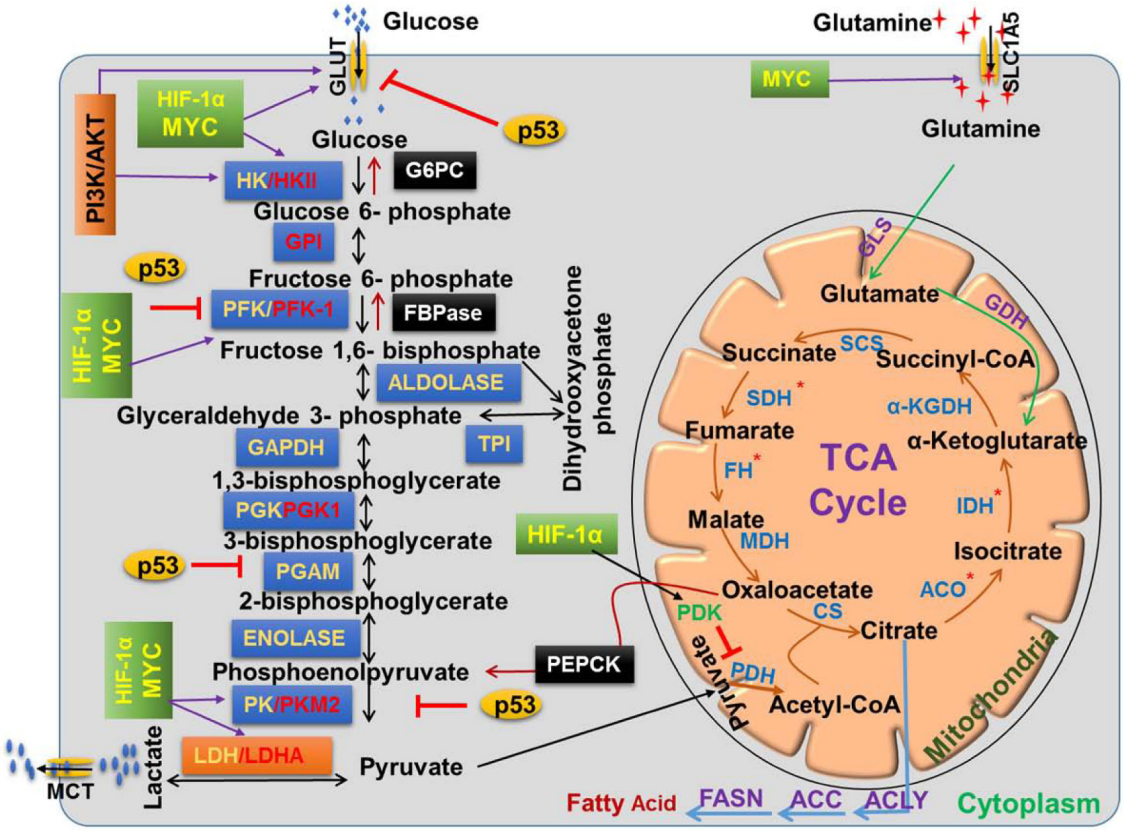

Figure 1: Dysregulation of glucose metabolizing enzymes in cancer cells.

During glycolysis, glucose is converted into pyruvate in a sequential enzymatic reaction. Pyruvate can shuttle to the mitochondria and inter into the TCA cycle for energy generation and/or biomass synthesis or alternatively converted into lactate by LDHA and secreted from cells. Many glycolytic enzymes are highly dysregulated (*red in color*) in several ways;, p53 and HIF-1α/MYC negatively and positively regulate expression of key glycolytic enzymes in cancer cells. Tumor cells display altered expression in some of the TCA cycle-related enzymes due to genetic mutations/alterations (*red asterisk*). Gluconeogenesis pathway generates glucose via antagonizing glycolysis. It has enzymatic overlap with glycolysis and utilizes seven out of ten enzymes of glycolysis along with three unique. Glutamine can also generate energy through the TCA cycle after converting into α-Ketoglutarate by enzymes glutaminase (GLS) and glutamate dehydrogenase (GDH). Citrate from the TCA cycle can be secreted out into the cytoplasm and utilized in fatty acid synthesis.

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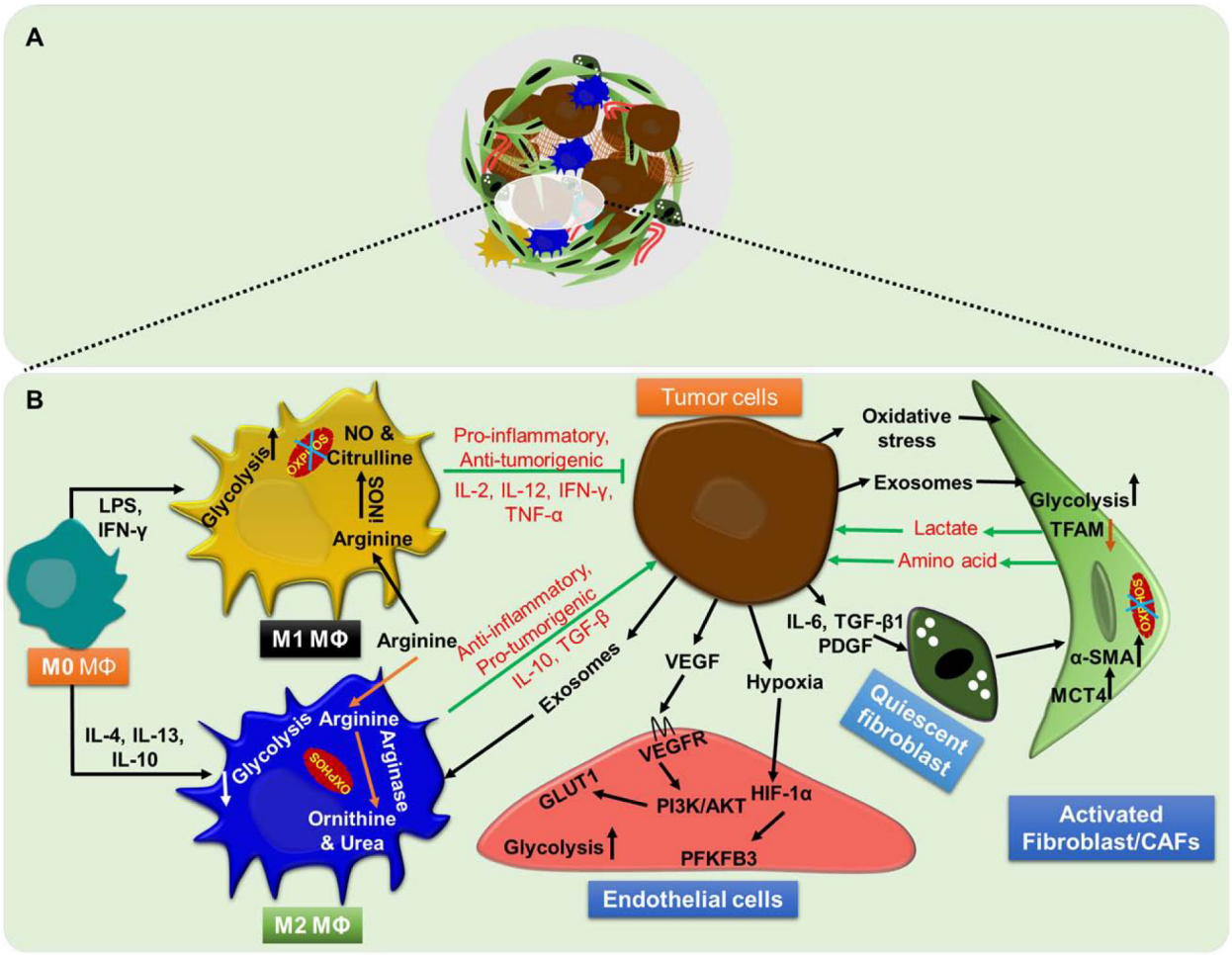

Figure 2: Metabolic reprogramming in stromal cells.

(A) Stromal cells, the pool of heterogeneous non-malignant cell types such as fibroblast, immune cells, and endothelial cells, are present within the tumor microenvironment. (**B**) Tumor cells metabolic reprogram surrounding stromal cells to meet their energy demand for sustaining growth, proliferation, aggressiveness and impairing host immune response.

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TABLE 1:

List of metabolic enzymes, their inhibitors, and underlying mechanism(s) of action.

Enzymes	Inhibitors	Mechanism of action	Refs
HK	3-Bromopyruvate (3BP)	Suppresses the production of ATP by alkylating HK-II	[92, 94]
	Lonidamine	Inhibits the activity of HK-II	[110]
PFK1	3PO	Indirect targets PFK-1 by inhibiting its allosteric activator, PFKFB3	[96–98]
PKM2	Tanshione IIA	miR122-mediated PKM2 downregulation	[101]
	Shikonin and its analogs	Inhibition via direct binding to PKM2	[111]
PDC/PDK	CPI-613	Inhibits PDC via activation of PDK	[103, 104]
	Dichloroacetate	Allosteric inhibition of PDK by binding to pyruvate regulatory site	[104]
LDH	FX-11	Non-specific/competitive inhibition at NADH binding site	[106, 112]
	Quinoline 3-sulphonamide	Inhibits LDHA by binding in the NADH pocket	[106]
PEPCK	3-Mercaptopicolinic	Competitive inhibition at the substrate-binding site and allosteric inhibition	[113]
	Dexamethasone	Induces gluconeogenesis by upregulating the PEPCK	[114]
G6Pase	Chlorogenic acid	Inhibits glucose-6-phosphatase transporter	[115]
Glutaminase	CB-839, BPTES, and trans-CBTBP	Inhibition through allosteric binding at GLS1 pocket	[116]
IDH	Ivosidenib (AG-120)	Rapid-equilibrium inhibitor of mutated IDH1	[117]
	Enasidenib (AG-221)	Non-competitive, allosteric inhibition of mutatedIDH2	[118]