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Drivers of Glucose and Glutamine Metabolism Reprogramming in Tumor Cells and Their Potential as Target for Cancer

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Abstract

Malignant cells undergo a metabolic transformation to satisfy the demands of growth and proliferation. This metabolic reprogramming has been considered as an emerging hallmark of cancer. It is well established that most normal cells get energy first *via* glycolysis in the cytosol that is followed by mitochondrial oxidative phosphorylation (OXPHO) under aerobic conditions but when oxygen is scarce, glycolysis rather than OXPHO for energy supply. However, cancer cells prefer to perform glycolysis in the cytosol even in the presence of oxygen, a phenomenon first observed by Otto Warburg and now famously known as ''Warburg effect'' or ''aerobic glycolysis''. Such reprogramming of glucose metabolism has been validated within many tumors, and increased glycolysis facilitates biosynthesis of biomass (e.g., nucleotides, amino acids and lipids) by providing glycolytic intermediates as raw material. Besides the dysregulation of glucose metabolism, metabolic reprogramming in cancer cells has been characterized by aberrant lipid metabolism, amino acids metabolism, mitochondrial biogenesis, and other bioenergetics metabolic pathways. However, the two noticeable characteristics of tumor cell metabolism are the Warburg effect and glutaminolysis, which, respectively, demonstrate the dependence of tumor cells on glucose and glutamine. Investigation on these metabolic changes would uncover fundamental molecular events of malignancy and help to find better ways to diagnose and treat cancer. This review aimed at appraising recent findings related to the drivers of glucose and glutamine metabolism reprogramming, their crosstalk in cancer cells, and their potential in cancer therapy.

Keywords: Metabolic reprograming; Novel targets; Cancer

Introduction

Compared to normal cells, tumor cells show an essentially contrarily accustomed metabolism to find ways to proliferate, even though both types of cells use the same nutrients. In this regard, metabolic reprogramming in cancer is commonly characterized by two prominent changes in metabolism: reliance on glycolysis rather than oxidative phosphorylation (OXPHO) for oxidation of glucose and increased use of glutamine as an energy source [1-3]. Otto Warburg showed that cancer cells are addicted to glycolysis; they ferment glucose into lactate rather than committing into OXPHO, regardless of oxygen tension [4]. He postulated that defect in tumor cells mitochondria resulted in reduced OXPHO [5]. But, this is not the case, according to current understanding. They do, however, adapt their function to the needs of cell proliferation. Mitochondria, in addition to acting as a hub for ATP production, it serves a significant role by synthesizing precursors required for proteins, lipids, and nucleic acids synthesis *via* Krebs's cycle [6-8]. Moreover, recent studies that aimed at analyzing the metabolic flux of tumor cells revealed that the Krebs's cycle can feed on glutamine instead of acetyl-CoA generated from pyruvate *via* glycolysis pathway [3,9,10]. It could be because of the form of cancer cells pyruvate kinase M2 (PKM2) that leads uncoupling of glycolysis and the Krebs's cycle as it acts as a rate limiting step in coupling the two pathways coupling of. Besides, it could also be because of inactivation of pyruvate dehydrogenase (PDH) enzyme (that is responsible for the conversion of pyruvate to acetyl CoA so as to join the Krebs's cycle) by pyruvate dehydrogenase kinases (PDK), known to be over-expressed in cancer cells [11,12-15]. To this end, in the following sections recent findings related to the drivers of glucose and glutamine metabolism reprogramming, their crosstalk in cancer cells, and their potential as cancer therapeutic strategy will be reviewed.

Underlining mechanisms

The fundamental mechanisms that lead to change in cancer cell metabolism continue to be clarified, but, existing literatures pointed out that alterations in numerous signaling pathways and altered expression and mutation of metabolic enzymes are central in mediating the unusual metabolic behavior of cancer cells [16-18].

Aberrant signalling pathways

Proliferating cells, i.e. both cancer cells and normal cells exhibit metabolic reprogramming, but, in normal cells, growth factor (GF) signaling-induced alterations to metabolism are responsive to environmental signals and rapidly down-regulated if circumstances are unfavorable for growth [16]. In contrast, in tumor cells, internal and external cues turn out to be decoupled, owing to up-regulation of oncogenic signaling pathways and/or down regulation of tumor suppressor signaling pathways [17] (Figure 1).

The Phosphoinositide-3-Kinase (PI3K) pathway

PI3K is one of the most commonly rearranged signaling pathways in human cancer cells [19]. It could be because of mutation in phosphate and tensin homolog (PTEN), a tumor suppressor gene that inhibits the PI3K pathway [20]. Besides, mutations in the components of the pathway itself have also been associated with PI3K activation [21]. Abnormal signaling through receptor tyrosine kinases (RTK) upstream to the PI3K pathway have been also associated with aberrant activation of the PI3K pathway [20].

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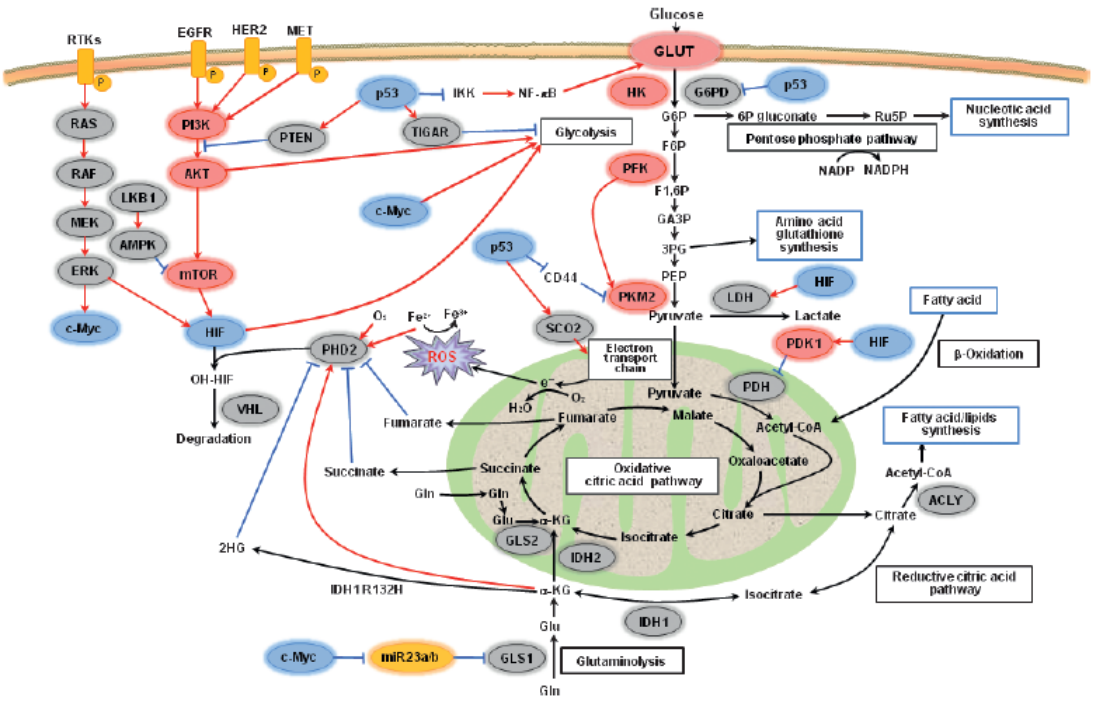

Figure 1: Signaling networks and their regulation of metabolism in cancer cells. It shows various aspects of energy metabolism regulation, including glycolysis, TCA cycle, pentose phosphate, glutaminolysis, fatty acid biosynthesis pathway, PI3K and RAS-MAPK signaling cascade. Three transcription factors, HIF-1, c-Myc and p53, are key regulators and coordinate regulation of cancer metabolism in different ways. 2HG: 2-Hydroxyglutarate; 3PG: 3-Phospho-Glycerate; 6P gluconate: 6-Phospho-Gluconate; a-KG; a-Ketoglutarate; ACLY: Acetyl-CoA by ATP-citrate lyase; AKT: v-akt Murine thymoma viral oncogene homologue; AMPK: AMP-Activated Protein Kinase; CD44, is a glycoprotein; EGFR: Epidermal Growth Factor Receptor; F1,6P: Fructose-1,6-Bisphosphate; F6P: Fructose-6-Phosphate; G6P: Glucose-6-Phosphate; G6PD: Glucose-6-Phosphate Dehydrogenase; Gln: Glutamine; GLS: Glutaminase; Glu: Glutamic Acid; GLUT: Glucose Transporter; HER2: Human Epidermal Growth Factor Receptor Type 2; HIF: Hypoxia-Inducible Factor; HK: Hexokinase; IDH: Isocitrate Dehydrogenase; IKK: Nuclear Factor-j Light-Chain-Enhancer of activated B cells kinase; LDH: Lactate Dehydrogenase; LKB1: Liver Kinase B1; MET: Hepatocyte Growth Factor Receptor; Mtor: Mammalian target of Rapamycin; NF-jB: Nuclear Factor-j Light-Chain-Enhancer of activated B cells kinase; OH: Hydroxy; P: Phosphate; PDH: Pyruvate Dehydrogenase; PEP: Phosphoenolpyruvate; PFK: Phosphofructokinase; PHD2: Prolyl Hydroxylase 2; PI3K: Phosphatidylinositol 3-Kinase; PKM2: Pyruvate Kinase Isozyme Type 2; PTEN: Phosphate and Tensin Homolog deleted on chromosome 10; RAF: Regulation of Alpha-Fetoprotein; RAS: Rat Sarcoma Virus Peptide; ROS: Reactive Oxygen Species; RTK: Receptor Tyrosine Kinases; Ru5P: Ribulose-5-Phosphate; SCO2: Synthesis of Cytochrome C Oxidase 2; TCA: Tricarboxylic Acid; TIGAR: Tp53-Induced Glycolysis and Apoptosis Regulator; VHL: Von Hippel–Lindau tumor suppressor, adapted from Song [17].

AKT1 is the effector downstream of activated PI3K pathway. Then, AKT1 directly affects cellular metabolism like stimulation of glycolysis possibly *via* up regulating glucose transporters proteins expression and membrane translocation, as well as by activating crucial glycolytic enzymes *via* phosphorylation as shown in Figure 1 [17,22]. Besides, its direct effect AKT1 indirectly involved in cancer cell metabolic reprograming by stimulating signaling through mammalian target of rapamycin (mTOR) [23]. Activation of mTOR has been associated with activation of transcription factors such as hypoxia-inducible factor-1 (HIF1), that leads to HIF1-dependent metabolic changes as shown in Figure 1 and Table 1 [17,24,25].

Liver Kinase B1 (LKB1)/Adenosine Monophosphate–Activated Protein Kinase (AMPK) pathways

The AMPK is a heterotrimeric serine/threonine protein kinase and an ATP sensor that regulates metabolic activates, directed at maintenance of cellular energy and viability [26]. AMPK activity is controlled by adenylate levels in the cells. For instance, AMP is a direct agonist of AMPK, and AMPK activation depends upon AMP: ATP ratio levels and conditions of metabolic stress such as nutrient deprivation or hypoxia, when ATP levels decline and the AMP and ADP levels increase [27]. Low glucose causes energetic stress in cells, leading to structure changes that promote phosphorylation of AMPK at Thr172 of the α-subunit and suppression of Thr172 de-phosphorylation by phosphatases [26]. Activated AMPK then directly phosphorylates several downstream substrates to impact energy metabolism and growth, stimulating gene expression for extensive changes in metabolic programming, suppressing protein synthesis, and stimulating fatty acid oxidation to replenish ATP [26,27]. For instance, AMPK directly phosphorylates peroxisome proliferator activated receptor gamma (PPAR-γ) coactivator-1-α (PGC-1α), a transcriptional coactivator that controls several metabolic genes and mitochondria formation [28]. AMPK may also promote acetylation and stability of p53 through inactivation of SIRT1, a p53 deactylase, *via* AMPK-mediated phosphorylation at Thr 344. It also inhibits growth and proliferation, increases OXPHO to preserve ATP, and can target various downstream metabolic pathways such as the mTOR pathway (Figure 1) [17,29,30]. Meanwhile, in addition to adynalate levels in cells, LKB1 also involved for activation of AMPK, especially under conditions of bioenergetic stress including glucose withdrawal [27,28].

However, loss of activity of AMPK has been associated with promotion of carcinogenesis *via* increasing the glycolytic pathway in tumor cells. This promotes a metabolic shift toward the Warburg effect [31]. However, loss of LKB1 expression in tumor cells reduces the AMPK signaling, making cells more sensitive to low nutrient level, and leading to unregulated metabolism and cell growth in energetically

stressful conditions [27,32-34]. This might promote tumorigenesis, as it leads to elevated glucose and glutamine flow, rising ATP levels, and a metabolic switch to aerobic glycolysis.

Hypoxia-Inducible Factor-1

HIF1 has been recognized as a key mediator of metabolic response to hypoxia [9]. It is a heterodimer composed of constitutive, stable β subunits and unstable α subunits, which are synthesized yet, degraded under presence of adequate oxygen due to the sequential action of oxygen-dependent prolyl hydroxylases (PHDs) and the VHL ubiquitin ligase (Figure 1). It functions as a transcriptional activator and enhances expression many oncogenes, including growth factors such as vascular endothelial growth factor (VEGF), which promotes angiogenesis; epidermal growth factor (EGF); insulin like growth factor-2 (IGF-2); transforming growth factor beta (TGF-β) [35-37], which stimulates growth and cell survival, and most importantly reprogram energy metabolism as shown in Table 1 [17].

Myc

Myc stimulates energy generation and precursor synthesis required for fast proliferation tumor cells [23]. Similar to HIF, Myc reprogram energy metabolism by altering target gene expression (Table 1).

p53

p53 plays an essential part in regulating the activities of glycolysis and OXPHOS (Table 1), in addition to its role in DNA damage response and apoptosis [38]. In general, p53 decreases the glycolytic rate, however, mutation or suppression of p53 frequently occurs in cancer, which results in losing control of its functions, thus promoting glycolysis. Surprisingly, mutant p53 inhibit mitochondrial respiration by down-regulating expression of cytochrome c oxidase 2 (SCO2) and Glutaminase 2 (GLS2) [39]. Moreover, it activates AKT and HIF, which are effectors downstream of PI3K [40].

Bcl-2 Proteins

Accumulated body of evidence has shown the involvement of the apoptotic mediator, B cell lymphoma/leukemia-2 (Bcl-2) proteins in reprogramming cancer cells metabolism [41-43]. A study done by Danial et al. [41] reported integration between glycolysis and apoptosis pathway due observation of mitochondria associated glucokinase (in the liver) with the pro-apoptotic protein Bcl-2/Bcl-xL-associated agonist of cell death (BAD). The study revealed that, glucokinase activation *via* direct interaction with BAD especially in response to phosphorylation of BAD by Akt, downstream of PI3K pathway. However, glucokinase inhibits BAD's pro-apoptotic activity when it bounds with BAD in its phosphorylated form. But, dephosphorylated BAD will dissociate from it, and able to interact with the anti-apoptotic protein Bcl-2/Bcl2-like 1, L isoform (Bcl-xL) and stimulate programed cell death. In this regard, binding of BAD to mitochondria associated glucokinase stimulate glucokinase and glycolysis activity that could be considered as one driver of metabolic reprograming in cancer cells, in addition to preventing its pro-apoptotic functions [42-44].

Furthermore, a pro-apoptotic BH3-containing protein known as damage protein (NOXA) also play a part in metabolic control. According to a study done by Lowman et al. [45], when there is elevation in of glucose level, NOXA will be phosphorylated by cyclin dependent kinase 5 (CDK5) that leads to localization of this pro-apoptotic protein with in the cytoplasm and making it unable to accomplishing its pro-apoptotic functions. As the study found out the protein rather form complex with the anti-apoptotic Bcl-2 protein myeloid cell leukemia-1 (Mcl-1) and stimulates improved glucose metabolism and enhances metabolism *via* the PPP, favoring synthesis ribose sugar and NADPH.

Pathways	Target genes	Transcription factors
Transporter	Glucose transporter 1	HIF, c-Myc & p53
	Glucose transporter 2	c-Myc
	Glucose transporter 3	HIF & p53
	Glucose transporter 4	c-Myc & p53
Glycolysis	Hexokinase 2	HIF, c-Myc & p53
	Phosphofructokinase 1	HIF & c-Myc
	Aldolase A	HIF & c-Myc
	GAPDH	HIF & c-Myc
	Phosphoglycerate kinase 1	HIF & c-Myc
	Phosphoglycerate mutase	p53
	Enolase 1	HIF & c-Myc
	Pyruvate kinase M2	HIF & Myc
	Lactate dehydrogenase A	HIF & c-Myc
Pentose phosphate	Transketolase	HIF
	Transketolase-like protein 2	HIF
TCA cycle	Pyruvate dehydrogenase kinase 1	HIF & c-Myc
	Glutaminase 2	p53
Others	Carbomyl phosphate synthetase aspartate	c-Myc
	transcarbomylase & dihydroorotase	
	Serine hydroxymethyltransferase	c-Myc
	Fatty acid synthase	c-Myc
	Ornithine decarboxylase	c-Myc

Table 1: Target genes of HIF, c-Myc and p53 associated with energy metabolism [17].

Furthermore, subsequent studies showed that over expression of NOXA in tumor cells, and over activity of CDK5 to promote tumor growth and survival, specifically in thyroid and neuroendocrine tumors [46,47].

Metabolic enzymes

In addition to activation of oncogenes and loss of tumor suppressor pathways, mutations in key metabolic enzymes as well as preferential expression of specific isoforms of metabolic enzymes can provide cancer cells a mechanism to select for metabolic alterations during tumorigenesis [3,8,48].

Pyruvate Kinase M2

Recent studies reported that, PK plays a crucial role in reprogramming of glycolytic metabolism. Four mammalian PK isoenzymes (M1, M2, liver isoform (L) and RBC isoform (R)) have been identified and distributed in diverse cell types [49]. The muscle isoform (PKM1) is a constitutively active tetrameric form that is found in normal adult cells, whereas PKM2 forms less active dimers as well as tetramers and found in differentiated tissues and normal proliferating cells [11].

To form the active tetramer, PKM2 requires fructose-1, 6-bisphosphate (F-1, 6 BP). Its tetramer form has high affinity to PEP and leads to improved production of pyruvate [50]. Meanwhile, studies done using cancer cells pointed out that, PKM2 conversion from the tetramer to less active dimer by phosphorylation mediated tyrosine kinases by at tyrosine 105 site in the enzyme that leads to a conformational change and dissociation of F-1, 6 BP. The PKM2 conformational change caused by phosphorylation leads to FBP release and conversion of the enzyme from the tetramer to the less active dimer form [51,52]. Hence, in tumor cells, PKM2 is predominantly available in its less active dimeric form, this leads to accumulation of glycolytic intermediates upstream to PK. Subsequently, it causes diversion of these intermediates into anabolic pathways which hasten active proliferation of cancer cells as shown in Figure 1 [17,50]. In contrast, replacement of embryonic and tumor isoform (PKM2) by PKM1 in tumor cell lines renders them less glycolytically active and diminishes tumor xenograft growth, suggesting that PKM2 might be responsible for the Warburg effect [52,53].

On the other hand, PKM2 has been shown to support tumor growth *via* "non-metabolic" attributes [54-56]. For instance, in a study done by Luo et al. [54], PKM2 shown to interact with HIF1α with in the nucleus and as reported by the study this interaction enhances transcriptional activity of HIF1α. This in turn leads to enhanced expression of target genes, including, GLUT1, PKM2, and LDHA. It is therefore, the study revealed a "positive feedback loop" mechanism that reprograms the glucose metabolism. Similarly, Yang et al. [55] showed that, activation of EGFR resulted in translocation of PKM2 into nucleus where it is associated with phosphorylated β-catenin to form a complex, which enhanced cyclin D1 and c-Myc expression. These findings underscore the importance of the integrated metabolic and non-metabolic functions of PKM2 in tumorigenesis.

Isocitrate Dehydrogenase (IDH)

IDH mutations can be seen as a case where a single point mutation (R132) affecting cellular metabolism is selected in cancer cells. In fact, IDH1 mutations were recognized in gliomas and acute myeloid leukemias (AML) [57,58]. It has been known that oxidative decarboxylation of isocitrate by non-mutant IDH1 generates α-ketoglutarate (α-KG) and NADPH, but not the case concerning the mutant IDH1 [1]. In this regard, Dang et al. [59] using in human malignant gliomas revealed that, the mutant IDH1 reduces α-KG to 2-hydroxyglutarate (2-HG) by consuming NADPH rather than generation. In AML, both the cytosolic IDH1 and the mitochondrial analogue IDH2 are commonly mutated [60]. One of the consequences of this change regarding tumorigenesis is that, stabilization of the oncogene HIF-1α, since for its degradation α-KG is required by PDH2 [35]. Moreover, 2-HG was shown to act as a competitive inhibitor of α-KG-dependent demethylases, including histone demethylases and the TET family of 5-methylcytosine hydroxylases, affecting CpG island hypermethylation. This links the oncogenic effect of IDH1 mutations to epigenetic regulation [61,62].

Succinate Dehydrogenase and Fumarate Hydratase

It has been known that, Krebs's cycle enzymes SDH and FH catalyze the conversion of succinate to fumarate and fumarate to malate, respectively. But, mutant form of these enzymes has been associated with carcinogenesis [63]. In this regard, Pollard et al. [64] reported frequent germline mutation in FH regarding familial cancer syndromes, renal, skin, and uterine cancers. In the same study, mutations in these enzymes caused accumulation of their substrate and these substrates i.e. fumarate and succinate ones accumulated can act as oncogenes when the traverse the inner mitochondrial membrane and enter the cytosol by dioxygenases and prolyl hydrolases, which are known to be involved in the degradation of the oncogene HIF-1α under normoxic environment [9].

Metabolic targeting for Cancer therapy

During the past decade, the metabolic rewiring of cancer cells has been viewed as a promising source of novel drug targets (Table 2) [9].

Targeting glucose metabolism

Targeting GLUTs, HK-II, PFK-1, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), PKM2, and Krebs's cycle mutant enzymes has been tried as part of development of anticancer drugs to modulate glucose metabolism in tumors [48].

Glucose transporters (GLUTs)

Several compounds, including, phloretin, WZB117 and fasentin has been demonstrated antitumor effects in preclinical studies by inhibiting GLUTs. However, selectivity of such drugs against tumors is under question because they are ubiquitously expressed in mammalian cells [3].

Hexokinase-II (HK-II)

Different types of tumors have been shown to overexpress HK-II compared with normal cells [1]. Accordingly, genetic deletion of the enzyme has been associated with slow progression and growth of cancer [65,66,67]. Moreover, 2-deoxyglucose (2-DG), a glucose analogue has been identified as a small molecule that inhibits HK and glycolysis according to in vitro and in vivo studies as reviewed by Xi et al. [68]. Furthermore, in study done by Zhu et al. [69] 2-DG showed in improved inhibition of growth, migration, invasion and cell cycle arrest when combined with metformin against ovarian cancer cell lines *via* p38 MAPK/JNK signaling pathway. O the other hand, in a recent study done by Ling et al. [70] showed that low-dose 2-DG can be used as a monotherapy to kill acute lymphoblastic leukemia (ALL) cells, and also as a glucocorticoid (GC) sensitizer to surmount GC resistance under normoxia. In this study addition of exogenous mannose, a sugar essential for N-linked glycosylation, has rescued 2-DG-treated ALL cells, revealing inhibition of N-linked glycosylation and induction of

Metabolic enzyme or transporter protein	Alteration in cancer cells	Consequence of alteration	Possible drivers	Example cancer types	Compounds under investigation	Ref.
Glucose transporters	Overexpression of GLUT-1, -3, -4 & -12	Facilitate glucose uptake by cancer cells	Over activity of MYC,AKT, HIF-1α, & LOF mutation of p53	Brain, breast, head, neck, bladder, renal, colon, lung & ovarian	Phloretin, WZB117, Fasentin	[3,105]
Hexokinase	Over expression of HK II	Facilitate glucose metabolism & also functions as a protective signaling molecule	Over activity of MYC' & AKT	Breast, colon, lung, liver, ovarian, pancreatic, glioblastoma, & thyroid	2-DG	[66-70]
Phosphofructokinase 1	Over expression of pfkfb-3	Increased production of F2, 6BP, a potent allosteric activator of PFK-1	Over activity of MYC' & AKT	Breast, colon, ovarian, thyroid, head, neck & squamous cell	PFK158	[72, 73]
Pyruvate kinase	Over expression of PKM2	Causes accumulation & diversion of glycolytic intermediates upstream to PK into anabolic pathways; enhances transcriptional activity of HIF1α	Over activity of HIF' EGFR & LOF mutation of p53	Lung, liver, colon, thyroid, kidney & bladder	TLN-232/CAP-232	[50-55]
Pyruvate dehydrogenase kinase	Over expression of PDK1-3	Reduce flux of pyruvate into mitochondria	Over activity of MYC, HIF-1α, & LOF mutation of p53	glioblastoma, breast, melanoma, cervical, colon, & ovarian,	DCA	[86-91]
Lactate dehydrogenase	Over expression of LDH-A	Prevent buildup of lactate inside cancer cell	Over activity of MYC, HIF-1α, & LOF mutation of p53	Liver, colon, lung, & pancreatic	FX11	[43,83, 84]
Monocarboxylate transporters	Over expression of MCT1 & MCT4	Facilitate lactic acid effuse from tumor cells	Over activity of MYC & LOF mutation of p53	Prostate, gastric, lung, breast, colon	α-cyano-4-hydroxy-cinnamic acid	[3, 85]
Glutamine transporter proteins	Over expression of SLC1A5 & LAT1	Sustain glutamine need of cancer cells	Over activity of MYC & LOF mutation of p53	Breast, colon, lung , melanoma, neuroblastoma, glioblastoma, & prostate	KM8094, BCH, GPNA	[94-99]
Glutaminase	Over expression of GLS1	Maintain a functioning TCA cycle	Over activity of MYC, KRAS, Rho GTPases & LOF mutation of p53	Colon, breast, lung, cervix, brain; human B lymphoma, prostate, & acute myeloid leukemia	BPTES, CB-83958, & compound 968	[100-105]
Glutamate dehydrogenase	Over expression of GLUD	Maintain a functioning TCA cycle	Over activity of MYC	Gliomas, leukemias, breast, lung & colon	EGCG, R162	[15]
Isocitrate Dehydrogenase	GOF mutation of IDH1, & IDH2	Production of 2HG from α-KG & resulted in stabilization of HIF-1α	-	Gliomas & acute myeloid leukemias	AG-221	[57-60]
Succinate Dehydrogenase & Fumarate Hydratase	LOF mutations FH, SDH B, -C & -D	Increased succinate &/or fumarate causes stabilization of HIF-1α	-	Renal, skin, & uterine	-	[63,64]

2-hydroxyglutarate (2HG); α ketoglutarate (α-KG); Succinate Dehydrogenase (SDH); Fumarate Hydratase (FH); Isocitrate Dehydrogenase (IDH); Solute carrier family A1 member 5 (SLC1A5); L-type amino acid transporter 1 (LAT1); Glutaminase 1 (GLS1); Monocarboxylate transporters (MCT); Lactate dehydrogenase (LDH); 2-aminobicyclo-(2, 2,1)-heptane-2-carboxylic acid (BCH); gamma-l-glutamyl-p-nitroanilide (GPNA); bis-2-[5–phenylacetamido-1, 2, 4-thiadiazol-2-yl] ethyl sulfide (BPTES), Epigallocatechin gallate (EGCG); Glutamate dehydrogenase (GLUD); Loss of function (LOF); Gain-of-function (GOF)

Table 2: Altered enzymes and transporter proteins in glucose and glutamine metabolism and possible drivers in various types of cancers

ER stress as alternative one mode of action in addition to inhibiting glycolysis, for 2-DG to elicit cell death and sensitize GC resistance ALL cells.it is therefore, future clinical studies might holds promise for this small molecule as a successful bullet against cancer.

Phosphofructokinase 1 (PFK-1)

PFK-1, involved in the conversion of fructose-6-phosphate to fructose-1, 6-bisphosphate in glycolysis pathway, is allosterically inhibited by PEP, citrate, and ATP and activated by a high concentration of AMP, ADP, and fructose-2,6-bisphosphate (F-2,6-BP) [1]. Several studies reported that over-activity of this enzyme in numerous types of cancer and allowing enhanced flux of glucose into the glycolytic pathway, since it catalyzes the first committed step in glycolysis [3]. According to studies, the major reason for over activity of this enzyme could be increased expression of an isoform of the PFK/fructose-2, 6-bisphosphatase (PFKFB) family of enzymes known as PFKFB3 activity in cancer relies upon the generation of an allosteric activator of PFK1 that results in the production of fructose-2, 6,-bisphosphate (F2, 6BP), known to be a potent allosteric activator of PFK-1, as reviewed by Luo et al. [71]. In this regard, four isoforms of PFKFB, i.e. PFKFB1-4, were found to be encoded by pfkfb gene but according to studies pfkfb-3 is commonly overexpressed in human cancers, including breast, colon, ovarian, thyroid carcinomas, head and neck squamous cell carcinoma [72,73]. Moreover, PFKFB3 is unsatisfactorily expressed in normal cells; it is therefore, targeting PFKFB3 could be a hopeful approach in oncology [71]. Accordingly, heterozygous genomic deletion of the Pfkfb3 gene reduced the concentration of F2, 6BP, glucose uptake, glycolytic flux and growth of tumors in syngeneic mice [72].

On the other hand, PFKFB3 inhibitor 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) and its derivative 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK15), have been demonstrated to inhibit glycolysis and display strong anticancer activity in numerous human tumor xenograft models, like tongue carcinoma, gastric cancer and head and neck squamous cell carcinoma [73,74].

Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH)

GAPDH has been known to catalyze the first step of glycolysis pay-off phase and NADH generated at this step helps a critical role in the cellular redox balance and biomolecule synthetic pathways [3]. In addition, the enzyme has other functions other than glycolysis, such as posttranscriptional control of T cell effector according to a study done by Chang et al. [75]. In this regard, inhibiting this enzyme could have a potential for cancer therapy. Accordingly, numerous GAPDH inhibitors were tested for their antitumor activity but a pyruvate analog 3-Bromo-pyruvate (3-BrPA) has been demonstrated a promising activity in solid and hematological cancers [76,77].

Pyruvate kinase M2

It is known that PKM1 and PKM2 are two major muscle type isoforms of PK that are alternative splice products of the PKM gene. In different studies, PKM2 has been shown to be up-regulated in many tumors [53,78,79]. Accordingly, elevated expression of PKM2 has been associated with shorter recurrence free survival in pancreatic ductal adenocarcinoma (PDA) patients. In a study done by Calabretta et al. [80] switching PKM splicing by antisense oligonucleotides (that blocks polypyrimidine-tract binding protein, a key modulator of PKM splicing, correlated with PKM2 expression in drug resistant-PDAC cell lines) to favor the alternative PKM1 variant rescued sensitivity of DR-PDAC cells to gemcitabine and cisplatin, suggestive of PKM2 expression is required to resist drug-induced genotoxic stress.

Moreover, small molecule inhibitors of PKM2 like TLN-232/CAP-232 have been demonstrated anticancer activity [81]. However, inhibiting PKM2 could allow glycolytic intermediates to accumulate and feed biosynthetic pathways, resulting in tumor promotion. In this regard, PKM2 can be regulated by cellular oxidative stress and increase in intracellular ROS concentration causes inhibition of the PKM2 *via* oxidation of Cys358, promoting diversion of glycolytic intermediates into the PPP to generate sufficient reducing potential for detoxification of ROS [82]. It is therefore, inhibiting PKM2 as a cancer therapy is controversial.

Lactate Dehydrogenase and Monocarboxylate Transporters

It has been known that conversion of pyruvate into lactate is catalyzed by LDH in the last step of anaerobic glycolysis. In this regard, buildup of lactate inside a cell known to be damaging since it disturb the PH inside a cell [3]. Numerous chemicals has been tried to target LDH enzyme as well as the transporter protein that extrude lactate out of the cell known as MCT [48].

For instance, FX11, an inhibitor of LDH diminishes cellular ATP that in turn leads to elevation in oxidative stress and subsequent tumor death [83]. In the same regard, the compound oxamate has been also shown to inhibit LDH and enhances radio-sensitivity in nasopharyngeal carcinoma cells [84]. On the other hand, the two isoforms of MCT, i.e., MCT1 and MCT4 have been targeted by many compounds since they are over expressed in cancer cells. For instance, α-cyano-4-hydroxy-cinnamic acid has been shown to inhibit proliferation and induces apoptosis in human breast cancer cells [85]. However, additional studies are warranted to validate efficacy of such agents.

Pyruvate Dehydrogenase Kinase

It has been understood that PDK is a key regulator of PDH complex involved in conversion of pyruvate to acetyl-CoA inside the mitochondria [3]. This regulation is achieved *via* phosphorylation of PDH by PDK that result in reduced flux of pyruvate into the mitochondria, and enhanced generation of lactate [12]. In this regard, overexpression of different isoforms of PDK (PDK1-3)) has been recognized in numerous tumors so as to support aerobic glycolysis in cancer cells [86].

One of the most promising compounds that inhibit the activity of PDK and have shown in reduction of tumor growth and facilitating cancer death in different in vitro and in vivo studies is dichloroacetate (DCA) [87-89]. Furthermore, in a study done by Saed et al. [90] DCA induces apoptosis of epithelial ovarian cancer cells through a mechanism involving modulation of oxidative stress. Moreover, in a small clinical trial, DCA treatment has been shown to induce radiological regression of glioblastoma multiforme (GBM) in some patients, along with reduced proliferation and increased apoptosis of cancer cells [91]. It is therefore, targeting PDK with small molecule inhibitors could be one possible approach for the inhibition of aerobic glycolysis

Krebs's cycle mutant enzymes

As mentioned above, mutation in in the Krebs's cycle enzymes IDH, FH, and SDH have been identified in different cancer types [59,60]. Novel compounds like that target the gain-of-function activity of mutant IDH have recently been shown to have success in preclinical and clinical settings [92], however, inhibiting mutant FH and SDH with small molecules has been unrealistic because these are loss of function mutations [88]. Accordingly, AG-221, inhibitor of mutant IDH2 has been shown to decrease the production of 2HG and cause tumor cells to differentiate towards a more normal phenotype and it is early phase clinical trials [93].

Targeting Glutamine Metabolism

The idea of interrupting the supply or utilization of the conditionally-essential amino acid glutamine in order to fight cancer dates back several decades and is based on its high concentration in plasma as well as the selective vulnerability of a variety of malignant cells to glutamine depletion [12,14,15,38].

Glutamine Transporter proteins

It has been recognized that, solute carrier family A1 member 5 (SLC1A5) and L-type amino acid transporter 1 (LAT1) which are involved glutamine transport in the cell shown to be up-regulated in malignancies [94,95]. To inhibit glutamine uptake by tumor cells different compounds have been tested in vitro and in vivo [96]. In a study done by Hassanein et al. [97] aimed at evaluating SLC1A5 as a potential target and candidate biomarker predictive of survival and response to therapy, targeting was examined in a panel of NSCLC and human bronchial cell lines by RNA interference and by a small molecular inhibitor, gamma-l-glutamyl-p-nitroanilide (GPNA). In the study, inactivation of SLC1A5 genetically or pharmacologically has been shown to decrease glutamine consumption, inhibit cell growth, and also induce autophagy and apoptosis in a subgroup of NSCLC cell lines that overexpress SLC1A5. Moreover in the same study targeting SLC1A5 has been shown to decrease tumor growth in NSCLC

xenografts. Similarly, in a recent study reported by Kasai et al. [98] has been the anti-tumor efficacy of a novel anti- SLC1A5 humanized monoclonal antibody, KM8094 against gastric cancer by inhibiting glutamine uptake.

On the other hand, a study done by Imai et al. [99] using inhibitor of LAT1, 2-aminobicyclo-(2, 2,1)-heptane-2-carboxylic acid (BCH), demonstrated reduction in viability of on-small cell lung cancer cell lines as well as, co-administration of gefitinib with BCH reduced the viability of the cells more than either agent alone. The authors reported that inhibition of LAT1 reduced the level of phosphorylation of mTOR, p70S6K and 4EBP1.

Glutaminase (GLS)

It is known that GLS is required to generate glutamate from glutamine during glutamine metabolism is GLS [1]. GLS has been inhibited using small molecule inhibitors such as bis-2- [50–phenylacetamido-1, 2, 4-thiadiazol-2-yl] ethyl sulfide (BPTES), CB-83958 and compound 968 [100-102]. In these studies inhibitions has been shown to significantly suppress tumor growth in several experimental models including breast cancer and lymphoma. Moreover, a recent study done by Song et al. [103] demonstrated that, loss of GLS1 expression by RNAi shown to decrease proliferation and survival of colorectal cancer (CRC) cells due to decrease in ATP levels and increases ROS level.

However, in a study done by Cheng et al. [104] silencing of GLS inhibits cell proliferation but fails to eliminate glioblastoma cells in both in vitro and in vivo models. The same study found out that induction of a compensatory anaplerotic mechanism mediated by pyruvate carboxylase (PC), allows the tumors to use glucose-derived pyruvate instead of glutamine for anaplerosis. Furthermore, Phannasil et al. [105,106] reported that expression of PC in cancerous areas of breast tissue at higher levels than in the non-cancerous areas by examining the expression of PC using immunohistochemistry of paraffin-embedded breast tissue sections of 57 breast cancer patients with different stages of cancer progression. In this regard, dual targeting of both GLS and PC could produce synergistic activity in arresting growth of tumors having glutamine addiction.

Current Challenges and Future Perspectives

Realizing the intricate nature of metabolic links and how different tumors adjust these processes to satisfy their metabolic demands will be one of the most important challenges in exploiting cancer metabolism target for cancer therapy. In this regard, explicit knowledge regarding most feasible targets and there control and cross-talk at different levels of regulation will transform the efforts of current studies in to fruit i.e. producing a successful anticancer agent targeting cancer metabolism. The other issue that could be a challenge and should be addressed in the future is selectivity, because highly proliferating cells like T lymphocyte cells have similarity in metabolic profiles like cancer cells, it is therefore, understanding the critical difference between cancer and highly proliferating normal cells will have paramount importance in avoiding toxicity. On the other hand, combining metabolic inhibitors with the currently available drugs which have been associated with cell death *via* oxidative stress, might leads to synergistic effect by arresting pro-survival mechanisms *via* generation of ATP as well as reducing powers like NADPH *via* PPP.

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