

Enhanced metabolism as a common feature of cancer plasticity

Minireview

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Cancer cells often rely on glycolytic metabolism in order to fulfill high demands of ATP and macromolecules for the sustained growth and proliferation. However, glycolysis is not necessarily the main source of energy for all cancer cells. Some of them rather depend on glutamine or lactate that favor the utilization of oxidative metabolic pathway. Different employment rate of metabolism creates variable products that participate in the formation of environmental milieu, which in turn triggers broad spectrum of cellular signaling pathways leading to migration, invasion, or proliferation. In this review we discuss different metabolic pathways promoted in tumor cells and describe the possibilities of their targeting as therapeutic strategies.

Key words: tumor metabolism, glycolysis, glutamine, lactate, reactive oxygen species (ROS), hypoxia inducible factor 1 (HIF-1)

Tumor metabolism

Metabolism is dynamically regulated system that accommodates cell's demands [1]. Tumor metabolism is still only partially understood due to its complexity caused by differences between tumor types and heterogeneity of cells belonging to tumor mass. These variances are further incurred by accumulation of random genetic mutations and enhanced by pericellular conditions [2, 3]. Metabolic byproducts subsequently influence tumor microenvironment and can impact molecular or metabolic pathways of cells in paracrine or autocrine manner. Tumor cells are able to adapt to conditions of microenvironment and reprogram their metabolism according to their requirements.

From hypoxia to aerobic glycolysis

During the process of tumorigenesis, cells grow and proliferate regardless of extracellular signals [4, 5]. Increased proliferation in pre-malignant lesions leads to gradual decline of oxygen (O₂) concentration with rising distance from the

blood supply further supported by formation of an aberrant tumor vasculature. This results in considerable microenvironmental heterogeneity among cells within the proliferating tumor mass that enhances variability arisen from the genetic background of tumor cells. Emerging hypoxic regions form a niche, which selects for the cells capable of adapting to harsh conditions of microenvironment through the metabolic shift to anaerobic glycolysis. Constitutively upregulated glycolytic metabolism, which persists even in normoxic conditions (Warburg effect) confers cells a strong selective growth advantage during tumor progression and metastasis [6]. Another understanding of Warburg's observation is that glycolytic metabolism precedes hypoxia which thus does not represent the principal factor guiding the metabolic shift [1].

Glycolysis seems energetically ineffective compared to oxidative phosphorylation, creating only 2 molecules of adenosine triphosphate (ATP) per 1 molecule of glucose, whereas full glucose oxidation generates 38 ATP [6, 3]. Although the glycolytic ATP production is very inefficient, under conditions of high glucose supply, it can outpace the ATP production from oxidative phosphorylation [7]. Secondly, oxidation of

the product of glycolysis, pyruvate, requires its import into mitochondria, activation of highly regulated pyruvate dehydrogenase (PDH) complex and is generally very slow. Pyruvate is therefore preferentially converted to lactic acid, which is in body fluids almost fully dissociated to lactate anion and proton [8]. In order to retain intracellular pH (pHi) neutral, protons (H⁺) have to be extruded from cell interior to extracellular space or neutralized by bicarbonate ions generated mostly by carbonic anhydrases [9]. Acidic extracellular pH (pHe) can subsequently become toxic to surrounding normal cells and support invasive and aggressive phenotype of cancer cells that are adapted and resistant to low pH environment [6, 10, 3]. Furthermore, acidic metabolites suppress functionality of and recognition by immune system [11], and can serve as mediators between cancer cells and cancer-associated stroma [12, 13, 14]. Proliferating cells require huge amount of macromolecules that can be produced by biosynthetic reactions, which require carbon and reduced nicotinamide adenine dinucleotide phosphate (NADPH). Glucose itself and metabolic intermediates supply carbon and NADPH wherein pentose phosphate pathway (PPP) plays a significant role [6, 3, 12]. Moreover, glycolysis ensures ability to resist fluctuating changes in O₂ concentration throughout stages of tumorigenesis [6].

It should also be noted that cancer cells employing aerobic glycolysis are not completely dependent on energy and substrates obtained from conversion of glucose through pyruvate to final product lactate, they rather partially convert pyruvate to acetyl coenzyme A (acetyl-CoA) that supplies cells with additional energy and precursors for anabolic reactions via the tricarboxylic acid (TCA) cycle [15, 16, 17].

Mediators of Warburg effect

Hypoxia-inducible transcription factor HIF-1 α is considered as the master regulator of the glucose metabolism [18, 19]. Its stabilization by hypoxia or by potent oncogenic events (e.g. RAS mutation) leads to induction of glucose transporters (GLUT-1/3), key glycolytic enzymes (9 out of 10), lactate dehydrogenase (LDHA) involved in the conversion between pyruvate and lactate [20], and also to modulation of the TCA cycle performance through a pyruvate dehydrogenase kinase 1 (PDK1). PDK1-mediated phosphorylation of PDHA1, a component of the PDH complex responsible for oxidation of pyruvate to acetyl-coA, results in a decreased flux of the glucose-derived pyruvate to the TCA cycle, thus supporting the glycolysis itself [21].

Metabolic reprogramming is very often connected with deregulation of the oncogenic transcription factor c-Myc. c-Myc contributes to the Warburg effect by stimulation of the glucose transporter and LDHA expression [19] and is involved in the transcriptional cooperation with HIF-1 α that leads to induction of hexokinase HK2 and PDK1 [22].

In addition, wild-type p53 directly downregulates glucose transporters, and is also involved in inhibition of the initial glycolytic reactions. Thus, p53 mutation or deficiency, a prevalent

feature of cancer cells, contribute to metabolic shift towards glycolysis [23].

Advantages of oxidative metabolism

The Warburg effect was initially explained by irreversible changes in mitochondria that render their oxidative metabolism non-functional [24]. However, it was later proven that most highly proliferative cancer cell lines do not have defects in oxidative metabolism [25, 4]. In some circumstances, mitochondrial function is even crucial for transformation [26] and metabolism of several cancer cell lines, such as HeLa, is supported by oxidative phosphorylation [27].

Mitochondrial metabolism is a key constituent of cancer cell proliferation and growth generating ATP, reactive oxygen species (ROS), NADH, FADH₂ and intermediates for macromolecular biosynthesis [28, 29, 30]. Indeed, the electron transport chain can function in the oxygen concentration as low as 0.5% [31].

The importance of oxidative metabolism in cancer cells, even with enhanced glycolysis, is supported by the role of c-Myc in stimulation of the mitochondrial biogenesis. In addition to direct binding of c-Myc to promoters of genes involved in the mitochondrial structure and function, c-Myc upregulates key mitochondrial transcription factor A (TFAM) that regulates mitochondrial transcription and mtDNA replication [32]. Interestingly, HIF-1 controls mitochondrial function and increases O₂ consumption in cells grown in hypoxia by switch of COX4 (cytochrome *c* oxidase) subunits [33]. Expression of COX4I2 isoform is upregulated by HIF-1, which simultaneously activates transcription of the mitochondrial protease degrading COX4I1 isoform LON [34]. Under a reduced availability of oxygen, COX4I2 optimizes the efficiency of respiration and its downregulation in hypoxic conditions reduces the number of viable cells, decreases ATP level and increases ROS production [34]. Surprisingly, the master regulator of hypoxia HIF-1 keeps the activity of cytochrome *c* oxidase, the terminal acceptor of O₂ in electron transport chain, to boost the ATP production from respiration in conditions of reduced substrate availability.

Glutamine and its versatility

Glutamine rather than glucose constitutes an important energetic source that supports cell survival, growth and proliferation in some cancer cell types [35, 36, 37, 38]. It represents the most abundant free amino acid in the body [39] and the main substrate for oxidation in the majority of transformed cells [40].

Upon entering cell cytoplasm by ASCT2 neutral amino acid transporter or SN2 transporters [36], glutamine is converted by glutaminase (GLS) to glutamate and ammonium that may cause changes in pHi and pHe values [40, 38, 41]. Released ammonia can function in acid resistance, which supports the role of glutamine in growth of cancer cells under acidic stress.

It has been shown that cancer cells consume more glutamine in acidic pH and GLS1 isoforms KGA and GAC are active in the pH as low as 6.0 [42]. Increased ammonia production in cancer cells is also important for the activation of autophagy, the process of self-digestion in order to recycle macromolecules to promote cell survival in the case of starvation [43].

Glutamate is turned into α -ketoglutarate (α -KG) by three enzymes – transaminases, l-amino acid oxidase, or glutamate dehydrogenase (GDH). Oxidation of α -KG by α -KG dehydrogenase to succinate supplies the classical TCA cycle thereby providing energy and metabolic intermediates as sources for cell building blocks exploitable in growth or proliferation [43]. Glutamine derived α -KG can also be involved in reductive carboxylation that leads to reverse production of citrate that is transported to cytoplasm and metabolized to acetyl-CoA and oxaloacetate important in lipid or amino acid synthesis [44, 43]. The reductive carboxylation is favored in hypoxic conditions [45].

In the process of glutaminolysis, partial oxidation of glutamine to lactate, α -KG is converted within the TCA cycle from succinate to fumarate and malate that leaves mitochondria and is further metabolized to pyruvate and lactate. Despite producing $FADH_2$ and $NADH_2$, glutaminolysis supplies NADPH that plays a critical role in maintenance of the cellular antioxidant capacity by regenerating the pools of ROS scavengers glutathione (GSH) and thioredoxin (TRX). NADPH is further important for the synthesis of lipids and metabolism of nucleotides [30, 46, 41, 47, 38].

Besides its direct participation in oxidative metabolism, glutamine contributes to redox homeostasis by taking part in the formation of GSH, one of the most abundant antioxidants in mammalian cells [48]. GSH is a tripeptide of glutamate, cysteine and glycine. Except for glutamate itself being a part of GSH, intracellular glutamate pools are important for the activity of X_c^- antiporter that exports glutamate and imports cysteine, another component of GSH [38]. The increased levels of GSH are important for resisting the oxidative stress associated with rapid metabolism and thereby support cell survival [4]. GSH is further involved in DNA repair, activation of transcription factors, cell cycle regulation, modulation of calcium homeostasis, or enzyme activity regulation [43].

As mentioned above, glutamine can regulate redox status by taking part in GSH formation. Glutamine, as a prominent stimulator of oxidative metabolism in cancer cells, further constitutes an important source of ROS production [49]. ROS-induced oxidative stress regulates several intracellular signaling pathways and processes including autophagy or apoptosis [50, 51].

Along with being the modulator of Warburg effect, c-Myc represents an important regulator of the glutamine metabolism. c-Myc activation causes glutamine addiction of glioma cells despite the presence of high amounts of glucose. This results in maintaining mitochondrial integrity and the TCA cycle function [36]. c-Myc directly induces the expression of glutamine transporters SLC7A5, or ASCT2 and is indi-

rectly involved in the induction of the GLS1, a first enzyme of glutaminolysis, by repressing its negative regulators – miRNA-23a and miRNA-23b [37].

Lactate as a substrate for oxidation

Lactate as a metabolic source initiating aerobic metabolism is beneficial for aggressive tumors as supported by the clinical observations of the positive association of elevated lactic acid levels with tumor progression, poor patient prognosis and overall survival [52, 53]. In fact, the amount of lactate in tumors ranges from 4-40 mM with average of about 15 mM compared to normal plasma concentrations 0.3-1.3 mM [54, 52, 55].

Existing examples of lactate utilization in normal tissues including muscle and brain may provide insights into its potential functioning in cancer cells. In muscle tissue, white muscle fibers exposed to intensive exercise produce (by anaerobic glycolysis) and export excessive amounts of lactic acid, whereas slow twitching red muscle fibers can upload lactate and utilize it as a substrate for oxidative metabolism [56]. Another metabolic cooperation was observed in the brain between glial cells (more specifically astrocytes) and neurons, with astrocytes preferentially employing glycolysis and neurons having the preference for lactate oxidation [57, 58]. As mentioned earlier, these patterns of lactate shuttling between glycolytic and oxidative cells in normal tissues point to possible similar cooperation between cells in tumor mass. Sonveaux, et al. (2008) observed preferential lactate import in normoxia and its use to fuel the TCA cycle by oxidative SiHa cervical cancer cell line compared to glycolytic WiDr colorectal cells that favored glucose as a metabolic substrate. Estimated model of *in vivo* metabolic symbiosis proposed by authors is lactate production by glycolysis in hypoxic tumor regions, its diffusion to and exploitation by oxygenated cells for respiration thus saving glucose for cells in the hypoxic core in order to preserve and potentiate aggressive tumor phenotype (Figure 1) [59].

It should be mentioned that lactate has to be converted to pyruvate in order to enter the TCA cycle and stimulate oxidative metabolism.

Elevated reactive oxygen species (ROS) as a hallmark of cancer

One of many outcomes of oxidative metabolism is the production of ROS. Mitochondria represent the largest contributor to cellular ROS levels, with eight known sites that are capable of producing superoxide [60]. Another major sources of ROS are NADPH oxidases that are involved in diverse cellular phenomena in which ROS perform a control function. Low levels of ROS have beneficial effects on cell proliferation by stimulating the post-translational modifications of kinases and phosphatases [61], but their excessive production causes detrimental oxidative stress that leads to cell death [62].

Elevated ROS levels are believed to be a hallmark of cancer [63], thus raising the need to control their actions. Cancer cells adapt to detrimental effects of ROS by producing antioxidant molecules, such as TRX and GSH and link them with the reducing power of NADPH [64]. NADPH production is therefore crucial for cancer cell survival also in the context of redox homeostasis and several metabolic pathways are involved in its production. Well documented pathways involve cytosolic conversion of the TCA cycle-derived malate and citrate to pyruvate and α -KG, respectively, thus linking glutamine-mediated supplementing of the TCA cycle to redox status maintenance. Third major source of NADPH comes from PPP that is also involved in the production of nucleotides for DNA synthesis [18].

Mitochondrial ROS are also tightly linked to the activation of hypoxia-response pathway. Recently, it was shown that the ROS-mediated oxidative stress leading to homodimerization of PHD2, as a result of disulfide bond formation, is linked to HIF-1 α accumulation [65]. Another hypothesis proposes indirect link between ROS and HIF-1 α – through the ROS-mediated upstream adjustments of the MAPK and PI3K signaling pathways, and possibly also of miRNA regulation [66]. Both of these growth factor-related pathways upregulate HIF-1 α through actions of their downstream target mTORC1, a major metabolic regulator, while ERK kinase activates also the overall transcriptional activity of HIF-1 α via phosphorylation of its co-activator CBP/p300 [67]. mtROS-mediated upregulation of HIF-1 α is supported by additional observation that hypoxia induces microtubule-dependent transport of mitochondria to the perinuclear region with related induction of the HIF-1 α transcriptional activity [68].

Biosynthetic pathways that stimulate tumor growth and proliferation

To allow for tumor cell proliferation, metabolic shift to the aerobic glycolysis has to be accompanied by elevated levels of subsidiary biosynthetic pathways. One part is represented by the cytosol-derived pathways, such as hexosamine biosynthetic pathway (HBP) or pentose phosphate pathway (PPP), that both stem from glycolysis. Second source of biosynthetic metabolites represent the TCA cycle-derived intermediates, as described below (Figure 2).

HBP consumes 2-5% of imported glucose and metabolizes it to UDP-*N*-acetylglucosamine (UDP-GlcNAc), which is used as a donor for O-GlcNAcylation or N-glycosylation of myriad of proteins [69]. In HBP, fructose 6-phosphate is converted to glucosamine 6-phosphate (GlcN-6P) by glutamine-fructose-6-phosphate aminotransferase (GFPT), while consuming glutamine. By subsequent series of reactions, HBP intermediates are linked to lipid (acetyl-CoA) and nucleotide (UDP) metabolisms [70]. Upregulation of HBP is documented in various cancer cell lines [71] and GFPT2, a rate-limiting enzyme of HBP, is also strongly induced in hypoxia [72, 73].

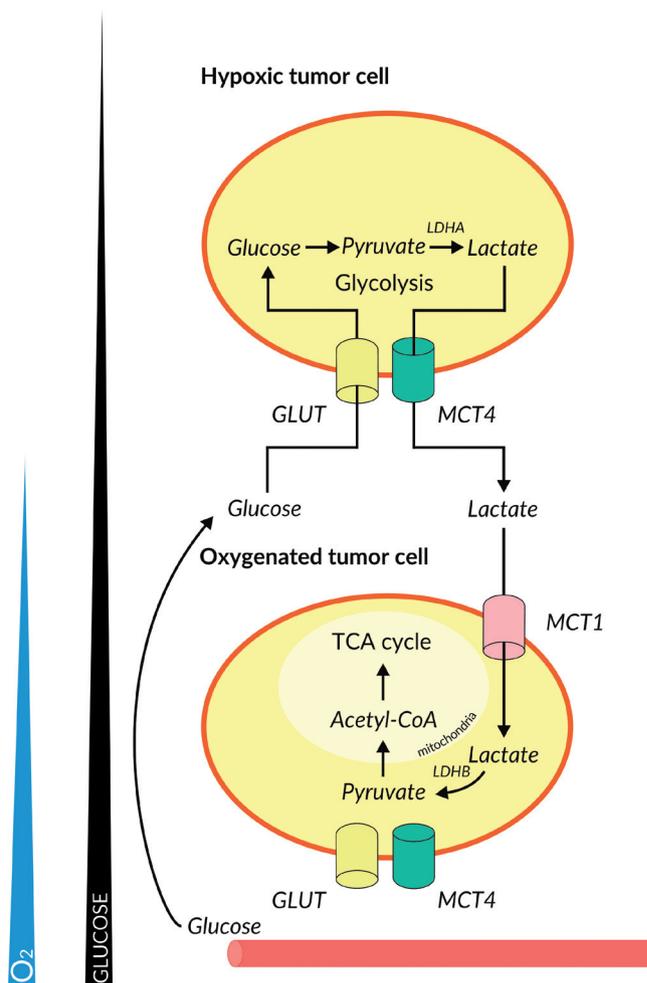


Figure 1. Estimated model of metabolic symbiosis in tumors. Hypoxic tumor cells prefer glycolytic use of glucose and convert it through pyruvate to the final product lactate by lactate dehydrogenase A (LDHA). Lactate is exported by MCT4 transporter to extracellular space, where it diffuses along its concentration gradient towards oxygenated tumor cells. Oxygenated cells preferentially import lactate by the major importer MCT1. Lactate is metabolized to pyruvate by lactate dehydrogenase B (LDHB), pyruvate enters mitochondria and is utilized in the TCA cycle for oxidative purpose. As a result, glucose can freely diffuse to distant regions containing hypoxic tumor cells and supply glycolysis. GLUT – glucose transporter, MCT – monocarboxylate transporter (adopted from the ref. 59).

Hypoxic pancreatic cancer cells that activate HBP pathway in a KRAS-dependent manner are therefore dependent on high glucose and glutamine supplies, important precursors that feed the HBP [72].

PPP consists of two mutually supportive pathways, an oxidative branch based on conversion of glucose-6-phosphate (G6P) through 3 irreversible reactions to ribulose-5-phosphate while generating NADPH and the non-oxidative branch composed of several bidirectional reactions connecting ketose- and aldose-phosphates with additional glycolytic intermediates, such as fructose-6-phosphate (F6P) and

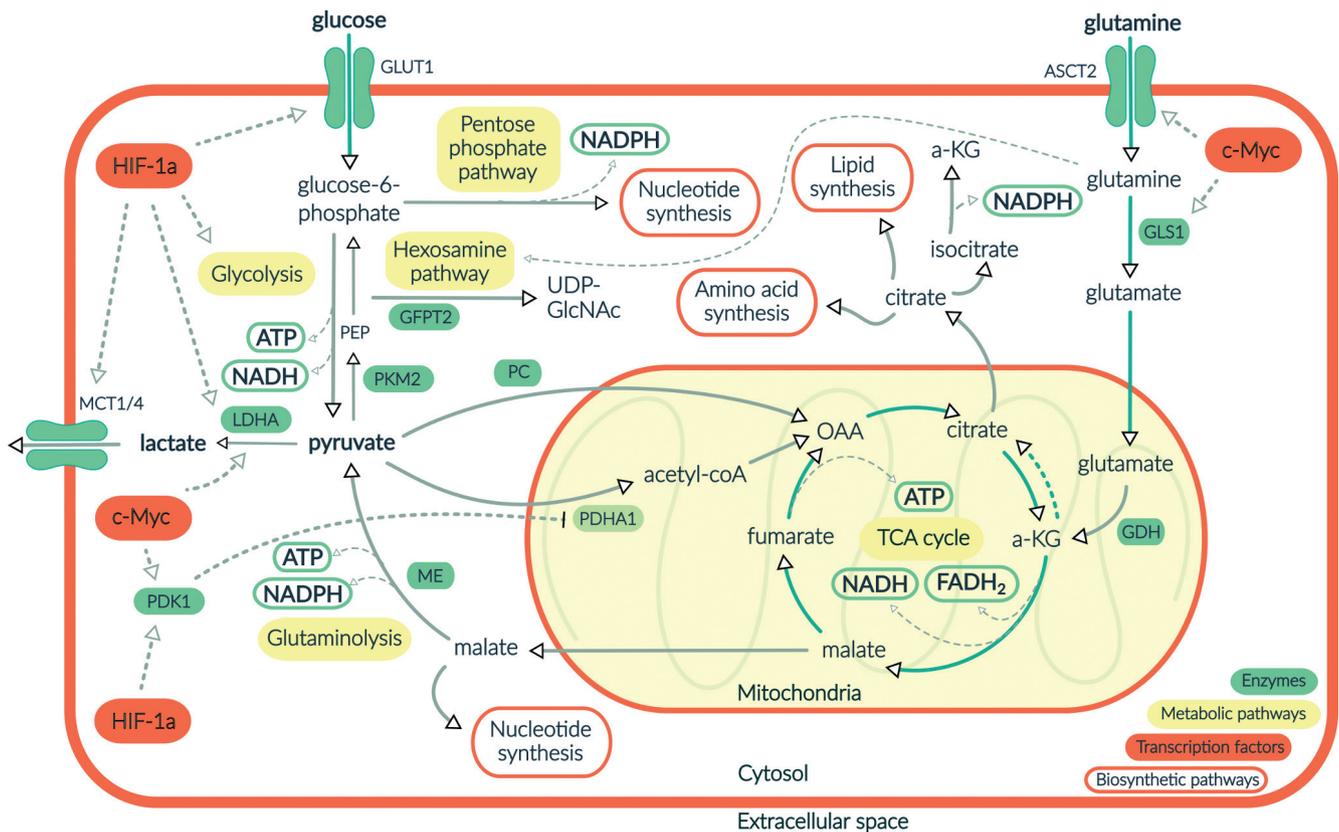


Figure 2. Biosynthetic pathways involved in cancer metabolism. Hypoxic cancer cells rewire their metabolism towards aerobic glycolysis. Pyruvate is preferentially converted to lactate and glycolysis itself fuels several cytosol-derived biosynthetic pathways – such as pentose phosphate and hexosamine pathways, that produce important precursors for synthesis of nucleotides, amino acids and lipids. Hexosamine pathway also provides the precursor for glycosylation of proteins. TCA cycle represents additional hub for biosynthesis that can be replenished by extracellularly-derived glutamine. Several important enzymes involved in biosynthesis are regulated by HIF-1 α and c-Myc transcription factors. They upregulate enzymes engaged in glycolysis, downregulate mitochondrial activity through inhibiting PDHA and c-Myc is also a major regulator of glutamine metabolism. Oxidative branch of PPP and several reactions, such as conversion of malate to pyruvate and conversion of isocitrate to α -KG also produce NADPH. With glycolysis-derived ATP and NADH, they can be used to fuel aforementioned biosynthetic pathways.

α -KG – alfa-ketoglutarate, PEP – phosphoenolpyruvate, UDP-GlcNAc – Uridine diphosphate *N*-acetylglucosamine, ASCT2 – ASC amino-acid transporter 2, GDH – glutamate dehydrogenase, GFPT2 – Glutamine fructose-6-phosphate aminotransferase 2, GLS1 – Glutaminase, GLUT1 – Glucose transporter 1, LDHA – Lactate dehydrogenase A, MCT1/4 – Monocarboxylate transporters 1/4, ME – Malate dehydrogenase, PC – Pyruvate carboxylase, PDHA – Pyruvate dehydrogenase E1 component subunit alpha, PDK1 – Pyruvate dehydrogenase kinase, PKM2 – Pyruvate kinase isozyme M2

glyceraldehyde-3-phosphate (G3P) [74]. Enzymes involved in PPP, that are frequently deregulated in cancer, are subjected to allosteric regulation by their products or other metabolites, thus allowing flexible metabolic response to diverse stimuli [75]. Glucose-6-phosphate dehydrogenase (G6PDH), a rate-limiting enzyme in the oxidative branch responsible for diverting the G6P into PPP is also activated by several signaling pathways, involving PI3K, RAS or SRC [76, 77, 78] whereas its negative regulation is under the control of the low NAD⁺/NADPH ratio. Key enzymes in the non-oxidative branch, transketolase (TKT) and transaldolase (TALDO) are also overexpressed in various cancers [79, 80] and in rapidly growing cancer cells generate the majority of ribonucleotides used in the DNA synthesis [81]. Additional control of the glucose flux through glycolysis, HBP and PPP is dependent

on the M2 isoform of pyruvate kinase (PKM2), a rate-limiting enzyme of the last glycolytic step – the conversion of phosphoenol pyruvate (PEP) to pyruvate [82]. Tumor associated expression of PKM2 with lowered enzymatic activity provides metabolic advantage via accumulation of upstream glycolytic intermediates capable of feeding the PPP [83, 84, 23, 64].

NADPH produced in the PPP serves as one of the most important sources of reducing power that feeds the glutathione-mediated antioxidant reactions, through ROS scavenging. It was demonstrated, that PPP derived NADPH counteracts the ROS-induced anoikis upon cell detachment [85]. NADPH produced in PPP is also linked to DNA and lipid synthesis [86].

As described above, second major branch of the biosynthetic pathways stems from the TCA cycle, because many basic

precursors for synthesis of amino acids, lipids and nucleotides derive from the TCA cycle intermediates [4]. Shunted TCA cycle intermediates create a truncated cycle that needs to be replenished. There are several ways how to supplement the TCA cycle. In some context, cells can enhance the activity of pyruvate carboxylase (PC) that is involved in converting the pyruvate directly to oxalacetate, a TCA cycle intermediate, or in other context, glutamine can serve as a potent precursor for the TCA cycle intermediates [87].

Therapy based on targeting tumor metabolism

Metabolism of cancer cells is often not dedicated to a single branch, but is rather intermediary, thus mirroring the metabolic adaptability of cells based on the availability of resources as well as the ability to cooperate in order to preserve and potentiate aggressive tumor phenotype. Accordingly, tumor cells dispose compensatory mechanisms upregulating glycolysis or mitochondrial metabolism when one of these metabolic pathways is suppressed. This constitutes an obstacle for cancer therapies targeting a single branch of metabolism. Therapeutic targets emerging as potentially suitable for inhibition of mitochondrial metabolism include poorly perfused tumors with limited glucose availability but sufficient amount of oxygen to sustain ATP generation; tumors highly addicted to mitochondrial metabolism lacking the ability of glycolytic compensation; and tumors exploiting both glycolysis and oxidative metabolism [30].

Several steps of glycolysis have been shown promising as therapeutic targets. Phloretin, that targets glucose transport across plasma membrane, inhibited tumor xenograft growth *in vivo* [88]. The therapies employing two inhibitors of enzyme hexokinase (catalyzing initial step of glycolysis) lonidamine and 2-deoxyglucose have been tested in clinical trials in several different solid tumors [89, 90]. TLN-232 suppresses pyruvate kinase that converts phosphoenolpyruvate into the product of glycolysis pyruvate and its effects have been studied in clinical trials with metastatic melanoma and renal cell carcinoma [91]. The reduction of pyruvate to lactate is regulated by enzymes including LDHA, which catalyses the formation of lactate from pyruvate, and PDK1 that blocks activity of PDH responsible for conversion of pyruvate to acetyl-CoA. Knocking down LDHA or inhibiting PDK1 by dichloroacetate (DCA) has been shown to reduce proliferation of cancer cells *in vitro*, with DCA being able to reduce the number of lung metastases of 13762 MAT cells injected into the tail vein of rats [92, 93].

As mentioned above, glutamine is a crucial amino acid important for ATP generation, macromolecule biosynthesis, or production of NADPH [30]. Many cancer cells are glutamine addicted and therefore targeting its metabolism is of a great interest in cancer therapy designs [40]. Compound 968 [94] and bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulphide (BPTES) [95] are inhibitors of GLS (an enzyme converting glutamine to glutamate). Compound 968 has been shown to delay the growth of lymphoma xenografts

expressing GLS [94]. BPTES impaired the growth of P493 lymphoma-derived xenografts [95]. The conversion of glutamate to α -KG can be inhibited by aminooxyacetate (AOA) that targets transaminases; or epigallocatechin gallate (EGCG) that suppresses GDH. AOA was efficient in reducing tumor growth in mice with breast adenocarcinoma xenografts and autochthonous neuroblastomas [96, 97]; the use of EGCG, a green tea polyphenol, suppressed the growth of neuroblastoma xenografts [98, 96, 41].

Metformin belongs to one of the most potential drugs selectively targeting metabolism of cancer cells. It lowers blood glucose and circulating insulin levels in diabetic patients [99]. Mechanisms of metformin mediated inhibition of cancer cell growth include reduction of circulating levels of mitogen insulin that upon binding to insulin growth factor receptor stimulates protumorigenic signaling pathways [100]. Second possible mechanism is inhibition of electron transport chain I leading to the decrease of ATP production in cells expressing organic cation transporter (OCTs) required for metformin import [30]. The combination of metformin with conventional therapies is currently evaluated in a number of clinical trials [101]. Other compounds inhibiting mitochondrial ATP production involve VLX600 [102], or gamitrinib [103]. The list of inhibitors of different metabolic pathways is reviewed in Tennant et al., 2010 [91].

It is important to mention that monotherapies could result in compensatory mechanisms and therefore, simultaneous targeting of different metabolic branches constitutes a promising strategy for cancer treatment.

Conclusion

To survive and progress, tumor cells need to adapt to ever changing conditions of tumor microenvironment. On the other hand, the constitution of tumor microenvironment is highly affected by products of cancer cell metabolism. Due to different tissue origins, metabolism among many cancer types is considerably heterogenous. Even a single tumor represents a diverse conglomeration of metabolic phenotypes as a result of increased metabolic plasticity compared to normal tissues. Tumor cells reprogram internal oncogenic signaling to converge and alter intrinsic metabolic pathways. Apparently, cancer cells need to establish rapid ATP generation for energy demands, increased biosynthesis of macromolecules and tightened maintenance of appropriate cellular redox status. Concurrent targeting of several steps of metabolic pathways therefore represents a promising therapeutic strategy to reduce cancer cell survival.

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