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## Glucose Metabolism and Cancer

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### 1. Introduction

An outstanding biochemical characteristic of neoplastic tissues is that despite ample oxygen supply, glycolysis is the dominant pathway for adenosine 5'-triphosphate (ATP) production, a phenomenon termed “the Warburg effect” (Warburg et al., 1927; Warburg, 1956). This aerobic glycolysis seems unexpected as one would imagine that cancer cells should have, given sufficient oxygen, adapted to utilize the complete oxidative phosphorylation to maximize ATP production. In addition, for producing same level of ATP, glycolysis would consume >15-fold more glucose, resulting in an addiction for glucose during active tumor growth. There must be a biological logic for cancer cells to prefer utilization of glycolysis for ATP production: they obtain and/or sustain growth advantage at the cost of an “addiction” to glycolysis. Mechanistically, there have been many hypotheses proposed to explain this phenomenon and two are more prominent: one is that by consuming excessive glucose, cancer cells may change the tumor’s microenvironment to gain growth advantage over normal cells; the second is that, to sustain a dominant glycolysis process, cancer cells alter the expression or functions of glucose metabolic enzymes, which may have resulted in additional changes that promote cancer development (Vander Heiden et al., 2009). A growing body of evidence has supported both hypotheses and will be reviewed here.

### 2. Altered glycolytic enzymes in cancer cells

In cancer cells, the activities or expression levels of many enzymes participating in glucose metabolism are altered, those involved in glycolysis in particular. The glycolysis commonly refers to the reactions that covert glucose into pyruvate or lactate (Figure 1). Usually, one or more isoforms of glycolytic enzymes have altered expression patterns or activities in cancer cells, which was previously reviewed (Herling et al., 2011; Porporato et al., 2011).

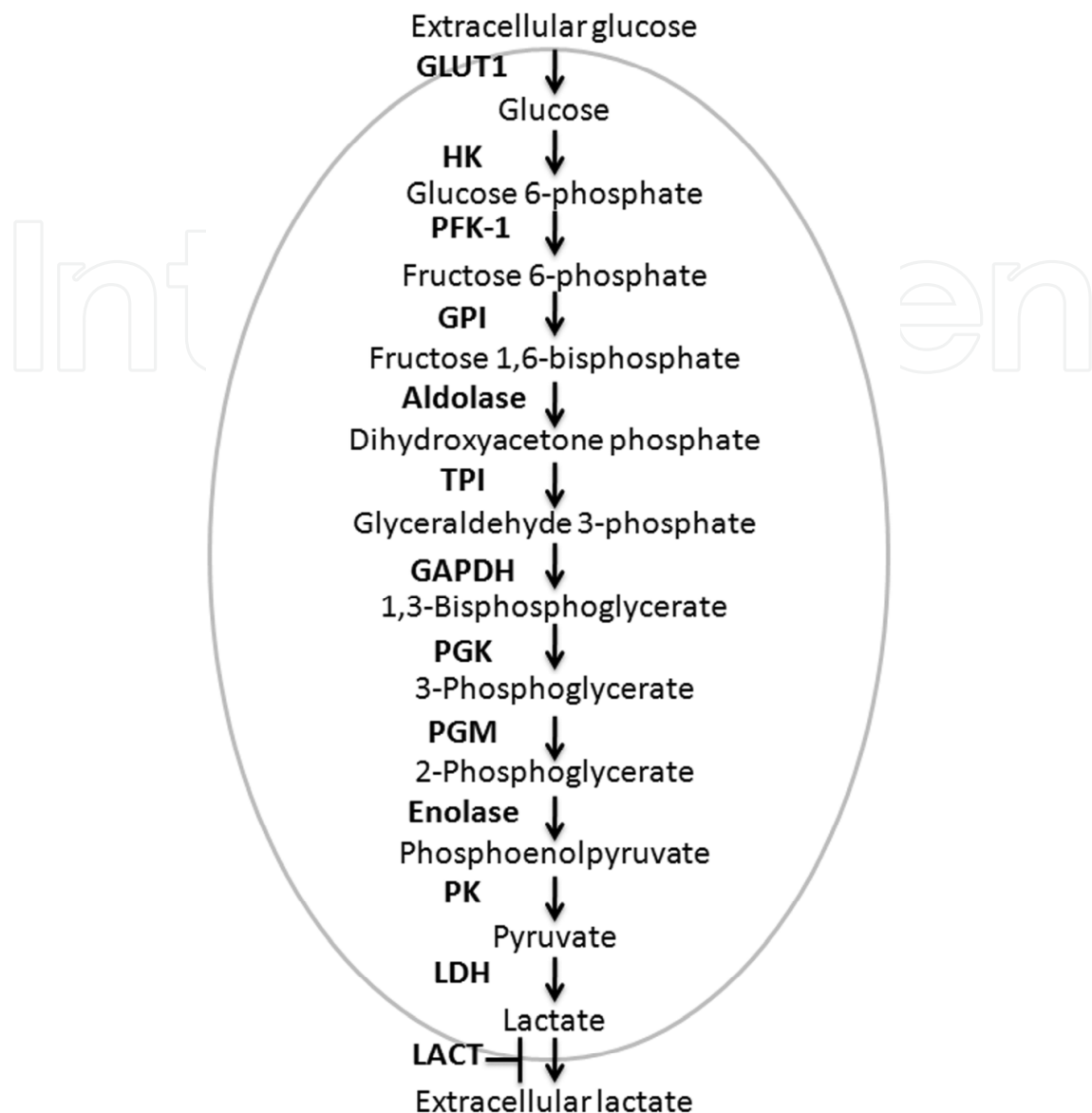


Fig. 1. Glycolysis in cancer cells

- GLUT1, an isoform of **glucose transporters** (GLUTs) is overexpressed in many types of human malignancies, whereas the insulin-sensitive GLUT4 is downregulated in cancer cells. The imbalanced expression of GLUT1 versus GLUT4 in cancer cells may have contributed to the insulin-independent glucose uptake in cancer cells. In addition, GLUT3 was also reported to be overexpressed in cancer cells (Smith, 1999; Medina and Owen, 2002; Noguchi et al., 1998).
- HK-2, an isoform of **hexokinase** that is one of the three rate limiting glycolytic enzymes, is overexpressed in cancer cells and was shown to contribute to the Warburg effect. The high glycolytic rate characteristic of hypoxic solid tumors is attributed to the overexpression of HK-2 (Mathupala et al., 2009; Wolf et al.).
- The expression level of the **glucose 6-phosphate isomerase** (GPI) has also been reported to be elevated in its mRNA level in different human cancer cell lines (Funasaka et al., 2005).

- The alteration of **phosphofructokinase-1** (PFK-1) in cancer cells is not at expression level, but at the level of the enzyme activity. PFK in cancer cells is less sensitive to the inhibition by its allosteric regulators such as citrate and ATP (Meldolesi et al., 1976). Additionally, the expression of all four genes of the **Phosphofructokinase-2** (PFK-2/FBPase/PFKFB) family is inducible by hypoxia, among which the gene encoding *PFKFB3* is highly expressed in several types of human neoplasm (Minchenko et al., 2005; Atsumi et al., 2002; Kessler et al., 2008).
- The expression of **aldolase** isoenzymes is downregulated in some cancer types such as hepatocellular carcinoma (Song et al., 2004) and upregulated in some other tumor types such as pancreatic ductal adenocarcinoma (Cui et al., 2009).
- **Triosephosphate isomerase** (TPI) was detected in the plasma of cancer patients (Robert et al., 1961) and autoantibodies against TPI was also detected in sera from breast cancer patients (Tamesa et al., 2009).
- **Phosphoglycerate kinase-1** (PGK-1) is overexpressed in majority of the pancreatic ductal adenocarcinomas and can also be detected in sera of patients with these tumors (Hwang et al., 2006).
- **Phosphoglycerate mutase** (PGM/PGAM) M type subunit (PGM-M) is overexpressed in many cancers including lung, colon, liver and breast (Durany et al., 2000; Durany et al., 1997).
- The expression of **Enolase 1** (ENO1) is upregulated at the transcriptional and / or translational level in multiple types of tumor including brain, breast, cervix, colon, eye, gastric, head and neck, kidney, leukemia, liver, lung, muscle, ovary, pancreas, prostate, skin and testis (Capello et al.). It is also differentially regulated at the post-translational level in cancer cells as compared with normal cells. ENO1 in tumor cells is subjected to more acetylation, methylation and phosphorylation than in normal tissues (Capello et al.). Specific acetylated residues of ENO1 were found in cervix, pancreatic, and colon cancers. Five aspartate and five glutamate residues were found to be specifically methylated in pancreatic cancer. Several serine and threonine residues were found to be specifically phosphorylated in leukemia, cervix, and lung cancers. Although ENO1 is phosphorylated at Serine 419 in both normal and malignant pancreatic tissues, this phosphorylated form of ENO1 is overexpressed in pancreatic cancer (Zhou et al., 2010).
- **Pyruvate kinase** has two isoforms, M and L, which have tissue-specific expression. Normal proliferating cells including embryonic cells and adult stem cells selectively express the M2 isoform (PKM2) (Reinacher and Eigenbrodt, 1981; Yamada and Noguchi, 1999). During tissue differentiation in development, embryonic PKM2 is replaced by tissue-specific isoforms. However, the tissue-specific expression pattern of PK is disrupted during tumorigenesis (Hacker et al., 1998). PKM2 is re-expressed and becomes the only predominant isoform in cancer cells (Mazurek et al., 2005).
- The **lactate dehydrogenase** (LDH) family of tetrameric enzymes catalyzes the pyruvate reduction into lactate. LDHs are formed by four subunits of two different isozymes of either LDH-H or LDH-M. LDH-H is encoded by the *LDH-B* gene and is ubiquitously expressed, and LDH-M is encoded by *LDH-A*. LDH-M has a higher *K<sub>m</sub>* for pyruvate and a higher *V<sub>max</sub>* for pyruvate reduction than LDH-H (Markert et al., 1975). Consequently, LDHs predominantly comprising of the LDH-M subunits drive the reduction of pyruvate to lactate; LDHs predominantly comprising of the LDH-H subunits drive the oxidation of lactate to pyruvate. Many types of tumor cells manifest a high expression of the *LDH-A* gene. Elevated expression of LDH5, which comprises of

four LDH-M subunits, is an unfavorable prognostic factor for many human malignancies (Koukourakis et al., 2003; Koukourakis et al., 2005; Koukourakis et al., 2009). In addition, the glycolysis process in cancer cells is reportedly to be associated with hypermethylation of the *LDH-B* gene promoter, which is linked to gene silencing (Leiblich et al., 2006; Thangaraju et al., 2009).

- Plasma membrane **lactate transport** (LACT) is facilitated by the family of proton-linked monocarboxylate transporters (MCTs) or by SMCT1, a sodium coupled lactate transporter. The MCT4 isoform is upregulated in many cancer types. The expression of MCT2, an isoform mainly implicated in lactate import, is decreased in tumor cell lines. SMCT1, also implicated in lactate import, is downregulated in a number of cancer types including colon, thyroid, and stomach (Herling et al., 2011; Porporato et al., 2011).

### 3. Glucose metabolic pathways switched by oncogenes and tumor suppressors

It has been long proposed that the altered expression or enzyme activities of glycolytic enzymes are regulated by oncogenes and tumor suppressor genes.

- The expression of GLUT1 has been demonstrated to be controlled by the hypoxia-inducible transcription factor HIF-1, c-Myc, and Akt (Chen et al., 2001; Osthus et al., 2000; Rathmell et al., 2003).
- The gene encoding HK-2, but not HK-1, is known to be a transcriptional target of HIF-1 (Rempel et al., 1996). It was later shown that HIF-1 cooperates with c-Myc to transactivate HK-2 under hypoxia (Kim et al., 2007). The phosphorylated form of HK-2 interacts with the voltage-dependent anion channel (VDAC) at the outer mitochondrial membrane (Bustamante and Pedersen, 1977; Nakashima et al., 1986; Gottlob et al., 2001). The interaction of HK-2 with VDAC interferes with the binding of the pro-apoptotic protein Bax to VDAC thus preventing the formation of the channel through which cytochrome c can escape from mitochondria to trigger apoptosis (Pastorino et al., 2002). Therefore, overexpression of HK-2 in cancer cells leads to a switch from HK-1 to HK-2 and offers a metabolic advantage by protecting cancer cells against apoptosis (Porporato et al., 2011).
- Overexpression of GPI can be induced by HIF-1 and VEGF (Funasaka et al., 2005).
- The expression of PFK-2 genes in tumor cells is shown to be regulated by Ras and src (Yalcin et al., 2009) and that of PFKFB3 is demonstrated to be induced by HIF-1, c-myc, ras, src, and loss of function of p53 (Minchenko et al., 2002). Among the four PFK-2 genes, PFKFB3 is the most significantly induced in response to hypoxia. Hypoxia-induced PFK-2 activity of human PFKFB3 is further enhanced through phosphorylation of the serine 462 residue (Marsin et al., 2002). This phosphorylation process may involve AMP-activated protein kinase (AMPK) and Akt (Shaw and Cantley, 2006; Yun et al., 2005).
- Although no evidence has suggested that the expression level of **Glyceraldehyde-3-phosphate dehydrogenase** (GAPDH) is altered in cancer cells, its expression has been demonstrated to be highly dependent on the proliferative state of the cells and can be regulated by HIF-1, p53, and c-jun (Colell et al., 2009; Colell et al., 2007).
- The gene encoding ENOA is a target of, and its expression is upregulated by, c-Myc (Sedoris et al. 2010). Notably, a growing body of evidence has suggested that ENOA



is a tumor-associated antigen (Capello et al., 2011). In patients of many different cancer types, including pancreatic, leukemia, melanoma, head and neck, breast and lung, anti-ENOA autoantibodies have been detected (Capello et al., 2011). In pancreatic cancer patients, the anti-ENOA autoantibodies are directed against phosphorylated Serine 419 (Tomaino et al., 2011). One study has shown that, in pancreatic cancer, ENOA elicits a CD4<sup>+</sup> and CD8<sup>+</sup> T cell response both in vitro and in vivo (Cappello et al., 2009). In pancreatic cancer patients, production of anti-ENOA IgG is correlated with the ability of T cells to be activated in response to ENOA (Cappello et al., 2009). In patients with oral squamous cell carcinoma, an HLA-DR8-restricted peptide (amino acid residues 321–336) of human ENOA recognized by CD4<sup>+</sup> T cell has been identified (Kondo et al., 2002).

- As described above, PKM2 is a predominant isoform of PKM in cancer cells. PKM2 is less active than other PKs but is however the only PK subject to regulation by the allosteric activator fructose-1,6-bi-phosphate (FBP) and possessing the capability to bind phosphotyrosine proteins (Christofk et al., 2008). Binding of phosphotyrosine peptides to PKM2 leads to dissociation of FBP hence lowering the PKM2 enzyme activity, which may provide a link between cell growth signals and the Warburg effect given that many growth signals and oncogenic pathways involve tyrosine kinases. The unique feature of the PKM2 isoform provides a mechanism by which oncogenes regulate glycolysis and the Warburg effect, and offers an advantage in metabolic plasticity by equipping cancer cells with an exquisitely regulated switch between promoting ATP production and cell proliferation; and lowering the PKM2 activity upon growth signaling was proposed to allow efficient biomass building (anabolic) pathways branched from glycolysis (Christofk et al., 2008). It was suggested that PKM2 is regulated by HIF-1 at the transcriptional level (Discher et al., 1998). Recently, it was demonstrated that, after nuclear translocation, PKM2 cooperates with HIF-1 to transactivate genes, the products of which are involved in promoting the glycolysis and tumor angiogenesis (Luo et al., 2011). Despite these advancements, the regulatory mechanism of PKM2 in cancer cells is not fully understood.
- The expression of PGM/PGAM was found to be downregulated by p53 (Kondoh et al., 2005). Thus, loss of p53 function is anticipated to induce the expression of PGM/PGAM. Phosphoenolpyruvate, the substrate for PK in cells, transfers the phosphate to the histidine residue located in the catalytic center of the human PGAM1; however, this reaction occurs only in those PKM2-expressing cells but is independent of the PKM2 enzyme activity. Thus, histidine phosphorylation of PGAM1 may provide an alternate glycolytic step in proliferating cancer cells where low PK activity accompanies the expression of PKM2 (Vander Heiden et al., 2010b).
- LDH-A is a target gene of c-Myc and HIF-1 (Dang et al., 2009). Loss of LDH-A functions results in diminished cellular transformation, anchorage independent tumor growth under hypoxic conditions, or xenograft tumor growth (Shim et al., 1997).

Therefore, activation of oncogenes and loss of tumor suppressors are believed to underlie the metabolic switch in cancer cells. Many cancer associated gene products are involved, including c-Myc, NF- $\kappa$ B, Akt, and multiple types of tyrosine kinase including epidermal growth factors (EGFs) and insulin-like growth factor 1 (IGF-1) receptor (Levine and Puzio-Kuter, 2010). Several pathways have been shown to be important for the regulation of glucose metabolism including the PI3K-AKT-mTOR and c-Myc pathways and both have

HIF-1 as their downstream effector. Consistently, among the HIF-1 regulated genes, most are those encoding glycolytic enzymes (Semenza, 2003). The loss of PTEN and concurrent increase of Akt and mTOR lead to the HIF-1 activation and the Warburg effect (Arsham et al., 2002; Zundel et al., 2000).

Another oncogene, K-Ras, can alter glucose metabolism so as to provide tumor cells with a selective advantage. In cells with mutated K-Ras, GLUT1 is upregulated, leading to an augmented glucose uptake, glycolysis and lactate production. Interestingly, in these cells mitochondrial functions and oxidative phosphorylation are not compromised, which allows increased survival rate of the K-Ras mutant cells during glucose deprivation (Annibaldi and Widmann, 2010).

Loss of p53 functions also leads to the Warburg effect. As described above, p53 represses transcription of the genes encoding GLUT1 and 4, and induces transcription of the TIGAR gene, which in turn lowers the intracellular level of PFK/FBPase (Bensaad et al., 2006). In addition, p53 inhibits the PI3K-Akt-mTOR pathways. This appears to be mediated by the transcriptional targets of p53 including PTEN, IGF-binding protein 3, tuberous sclerosis protein TSC-2, and the beta subunit of AMPK (Feng et al., 2007). Conceivably, loss of p53 functions and subsequent loss of expression of these target genes lead to a high HIF level and establishment of the Warburg effect.

#### **4. Tumor “friendly” microenvironment attributed to altered glucose metabolism**

One would ask: what is the advantage for cancer cells to use energy-inefficient glycolysis under adequate oxygen supply. A potential advantage, as a result of Warburg effect, is high production of lactic acid due to enhanced glycolysis. Positive correlation between lactate serum levels and tumor burden in cancer patients has been well documented, implicating a role of acidic microenvironment in promoting tumor growth and development (McCarty and Whitaker, 2011).

First, accumulated evidence has suggested that acidic environment amplifies the capacity of invasion and metastasis of cancer cells. For instance, acid pretreatment of tumor cells enhance their ability to form metastases in tumor-transplanted mice (Rofstad et al., 2006). Consistently, it has been shown that increasing tumor pH via bicarbonate therapy significantly reduces the number and the size of metastases in a mouse model of breast cancer (Robey et al., 2009).

Second, the extracellular pH of solid tumors is significantly more acidic than that of normal tissues, thus impairing the uptake of weakly basic chemotherapeutic drugs (Raghunand et al., 1999). Several anticancer drugs such as doxorubicin, mitoxantrone and vincristine are weak bases that are protonated in slightly acid tumor microenvironments. The protonated forms of the drugs cannot easily diffuse across the plasma membrane and therefore their cellular uptake is suppressed. It has been demonstrated that the addition of sodium bicarbonate in the drinking water enhanced the anti-tumor effect of doxorubicin on xenotransplanted tumors presumably by enhancing the intracellular drug delivery through raising the pH of the extracellular milieu in mice (Raghunand et al., 1999). The reverse situation was also demonstrated in another study showing that glucose administration to mice led to a lower efficacy of doxorubicin on tumors presumably due to a decrease in the extracellular pH (Gerweck et al., 2006).

Third, acidic microenvironment inhibits anti-tumor immune response. For instance, lactic acid suppressed the proliferation and cytokine production of human cytotoxic T lymphocytes (CTLs) up to 95% and led to a 50% decrease in cytotoxic activity (Fischer et al., 2007). Activated lymphocytes themselves use glycolysis, which relies on the efficient secretion of lactic acid. Export of lactic acid from lymphocytes depends on a gradient between intracellular and extracellular lactic acid concentration. High extracellular acidity would diminish this gradient and block the secretion of lactic acid from lymphocytes. The accumulation of intracellular lactic acid eventually disturbs the glycolysis process hence affecting the activity of lymphocytes. Acidification similarly inhibits the activity of other immune cells such as dendritic cells.

## **5. Coupled biological and metabolic processes and the logic of a mammalian metabolic cycle**

Glycolytic enzymes have multiple cellular functions. For instance, GAPDH has been implicated in numerous non-glycolytic functions (Colell et al., 2007; McKnight, 2003). In 2003, we published a paper that describes the isolation and characterization of OCA-S, which is a transcription cofactor complex that directly stimulates the transcription of the histone H2B gene in an S-phase-specific manner (Zheng et al., 2003). Surprisingly, a key component of the OCA-S complex represents a nuclear form of GAPDH, which regulates H2B transcription in a redox dependent manner. LDH was later shown to be an essential OCA-S component as well and can exercise the enzyme activity to reverse in vitro inhibition of H2B transcription by converting NADH to NAD<sup>+</sup> in the presence of substrate pyruvate (Dai et al., 2008). Conceivably, the participation of these glycolytic enzymes in such a cell cycle event would subject cell cycle regulation to altered glucose metabolism in cancer cells, providing yet another mechanistic explanation of cancer growth and development. The “moonlighting” participation of the glycolytic enzymes in a cellular process would in theory impose a dynamic modulation of the redox status in the cellular compartment where this process is executed and subsequently affect the functions of other redox-sensitive proteins in the same intracellular compartment. Thus, in addition to histone expression, our study has suggested that other cellular processes including cell cycle regulation, DNA replication and damage repair are potentially all coupled through the redox signals (Yu et al., 2009). The coupling of these cellular processes is apparently crucial for the maintenance of chromatin integrity during cell cycle, and thus altered glucose metabolism in cancer cells potentially would disrupt the coupling of these processes and make cancer genomes more error-prone.

It is well delineated that in yeast, quite a few biological and metabolic processes are known to be compartmentalized in time, termed the yeast metabolic cycle (YMC) that is in sync with the cell cycle progression (Tu et al., 2005). The YMC has oxidative, reductive/building and reductive/charging phases, and the S-phase of yeast cell is synchronized with the most reductive stage of YMC. We subsequently found that the oxidative and reductive phases in mammalian cells are also synchronized with the cell cycle, and our study demonstrated that the free NAD<sup>+</sup>/NADH ratio fluctuated in a defined manner during cell cycle (Yu et al., 2009). At G1 phase, the intracellular NAD<sup>+</sup>/NADH ratio is high, suggesting that G1 cells maintain an oxidative status. Upon entering S phase, the ratio becomes lower, corresponding to a reductive status. When the cells exit S phase and enter G2 phase, the NAD<sup>+</sup>/NADH ratio becomes higher again. This oxidative status appears to be maintained



until cells enter the next S phase. This phenomenon has been dubbed mammalian metabolic cycle (MMC) for its similarity with YMC. The fluctuating  $\text{NAD}^+/\text{NADH}$  ratios in a mammalian cell cycle must reflect overall oscillatory cellular metabolism; whether and how glucose metabolism is synchronized with the cell cycle remains to be explored. Nonetheless, this synchronization must have been very precisely regulated. Conceivably, if glucose metabolism is altered, the cell cycle must be coordinately modulated, and vice versa. Therefore, cancer cells may have acquired the growth and proliferative advantage over normal cells through alteration in glucose metabolism.

## 6. Targeting glycolysis for cancer treatment

The aberrant metabolic pathways underlying the Warburg effect are being considered as novel targets for cancer therapy. Several strategies have been employed to target glucose metabolic pathways for cancer treatment.

**First**, inhibitors of glycolytic enzymes or glycolytic pathways are being searched to identify therapeutic agents that can inhibit cancer growth and development.

A number of small molecules have been reported to target glycolysis although none to date has been shown to have specific molecular targets. For example, 3-bromopyruvate, a highly active alkylating agent, was reported to target HK-2 and/or GAPDH (Dang et al., 2009). 2-deoxyglucose (2-DG) can be phosphorylated by HK-2, which in turn inhibits HK-2 (Ralser et al., 2008). It is also shown to be a GLUT inhibitor.

Many efforts have been made to identify specific inhibitors. Lonidamine has been described as a specific inhibitor of mitochondria-bound HK (Floridi et al., 1981) and has been tested in multiple clinical trials including a phase II study in combination with diazepam for the treatment of glioblastoma patients (Porporato et al., 2011). Unfortunately, none of these clinical trials have successfully shown its therapeutic benefit in terms of time-to-progression and overall survival (Oudard et al., 2003); one study showed its severe hepatic adverse effects.

Drugs that target more specific metabolic control points of glycolysis in cancer cells, such as PKM2 or LDH-A, warrant investigation as potential cancer therapies. gossypol/AT-101, a natural product and a non-specific LDH inhibitor that has more preferential inhibitory activity on malarial and spermoctye LDHs, has already been tested in human clinical trials for its anti-cancer effect (Porporato et al., 2011). A selective competitive inhibitor of LDH5, 3-dihydroxy-6-methyl-7-(phenylmethyl)-4-propylnaphthalene-1-carboxylic acid (FX11), has been identified through screening a library of compounds derived from gossypol (Yu et al., 2001). FX11 has been shown to suppress in vivo xenograft tumor growth of human B lymphoid tumor and pancreatic cancer cells (Le et al. 2010), providing a strong rationale for clinical development of therapeutic agents targeting LDH-A. Recently, *N*-Hydroxy-2-carboxy-substituted indole compounds have been identified as LDH5-specific inhibitors (Granchi et al., 2011).

Several clinical trials with the PKM2 inhibitor TLN-232/CAP-232, a seven amino-acid peptide, have been initiated. Encouraging preliminary results demonstrated that it is safe, well tolerated, and may offer disease control (Porporato et al., 2011). New small molecule inhibitors of PKM2 were also screened. Among them, the most potent one resulted in decreased glycolysis and increased cell death in response to loss of growth factor signaling, supporting the feasibility and viability of targeting glucose metabolism as a novel strategy to treating human cancers (Vander Heiden et al., 2010a).

Conceivably, ENOA, as a tumor-associated antigen with an ability of eliciting both B cell and T cell immune response (Capello et al., 2011), is an ideal target of cancer vaccine and immunotherapy. Comparing to small molecule inhibitors, immunotherapy offers superior target specificity and may be used as an alternative approach to target other glycolysis enzymes.

**Second**, inhibition of glycolytic enzyme or glycolysis pathways serves as a strategy to enhance the sensitivity of tumor cells to conventional cytotoxic chemotherapy agents.

Inhibition of LDH-A has been shown to re-sensitize Taxol-resistant cancer cells to Taxol (Zhou et al.). 2-DG is another example. The safety of using it as an anti-cancer agent has been questioned notably because of brain toxicity (Tennant et al., 2010). However, it has a proven efficacy in sensitizing human osteosarcoma and non-small cell lung cancers to adriamycin and paclitaxel (Maschek et al., 2004). Recently, a Phase I clinical study for prostate cancer has defined a maximum tolerance dose of 45mg/kg for Phase II trials (Stein et al., 2010). It will be interesting to test whether 2-DG can enhance the efficacy of chemotherapy agents even if it cannot offer anti-cancer activity by itself at this dose level.

As aforementioned, chemosensitivity is enhanced by counteracting the acidification of tumor's microenvironment. Inhibitors of glycolytic enzymes may impose an alkalizing effect in tumor's microenvironment particularly at the tumor tissue level and thus may have a more specific and powerful role in enhancing the sensitivity of tumor cells to basic chemotherapy drugs. Major targets for counteracting the acidification of tumor's microenvironment include carbonic anhydrases (CA)-9 and -12, sodium-proton exchanger 1 (NHE1), sodium bicarbonate cotransporter (NBC), vacuolar ATPase (V-ATPase), sodium-potassium (NaK) ATPase, and MCT4 (Porporato et al., 2011). Indisulam is a leading compound for CA9 inhibition. It is a sulfonamide derivative and shown to inhibit CA9 at nanomolar concentrations (Abbate et al., 2004; Supuran, 2008; Owa et al., 2002). It has been tested in multiple clinical trials for the treatment of melanoma, lung, pancreatic and metastatic breast cancers and has not been found in the completed clinical trials to have antitumor efficacy as a single agent (Talbot et al., 2007). Girentuximab, a specific antibody targeting CA9, is now being tested in Phase III clinical trials for the treatment of clear-cell renal cell carcinoma (Reichert, 2011). Several inhibitors of membrane-bound V-ATPase have been reported to have antitumor activity in preclinical studies (Perez-Sayans et al., 2009). Other enzymes involved in the cellular export of protons are also studied as targets of anti-cancer therapeutic development. However, future studies should emphasize on combining anti-acidification therapies with cytotoxic chemotherapy or immunotherapy to achieve the effective anti-cancer treatment.

**Third**, combination of inhibitors of glucose metabolic enzymes with inhibitors of oncogenic pathways may result in synergistic anti-tumor effects.

Inhibitors of oncogenic pathways have been extensively tested for cancer therapy, with only moderate success in a few types of human cancers. Among them, inhibitors of the Ras pathway are essentially not effective. As K-ras mutated cancer cells have an enhanced survival when glucose is deprived, a combinatorial treatment with both glycolysis inhibitors and Ras pathway inhibitors may target Ras-mutated cancer cells more effectively and more specifically. Supporting this hypothesis, the hexokinase inhibitor 3-bromopyruvate was demonstrated to be highly toxic specifically to cancer cells with K-ras mutation, but not to

cancer cells with wild-type K-ras (Yun et al., 2009). BAY87-2243, which is a small molecule inhibitor of HIF-1 activity and of HIF-1 $\alpha$  stability, and EZN-2968, which is an antisense oligonucleotide targeting HIF-1 $\alpha$ , had been tested in clinical trials (Greenberger et al., 2008). Metformin is an AMPK-activating drug and is currently used for type-2 diabetes treatment. Epidemiological studies have shown reduced incidence of cancer in diabetic patients treated with metformin (Evans et al., 2005; Jalving et al., 2010; Libby et al., 2009). It is highly intriguing to test whether this clinically safe and known glucose metabolism modulating drug can enhance anti-cancer activity of cytotoxic chemotherapy and/or further lower the cancer recurrence following adjuvant chemotherapy. Similarly, other combination treatments with inhibitors of both glucose metabolisms and oncogenic pathways such as Akt, mTOR, etc. also warrant investigation.

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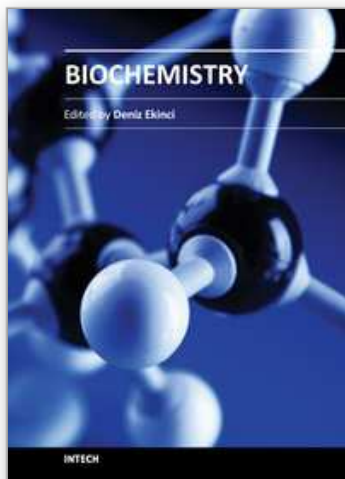
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Over the recent years, biochemistry has become responsible for explaining living processes such that many scientists in the life sciences from agronomy to medicine are engaged in biochemical research. This book contains an overview focusing on the research area of proteins, enzymes, cellular mechanisms and chemical compounds used in relevant approaches. The book deals with basic issues and some of the recent developments in biochemistry. Particular emphasis is devoted to both theoretical and experimental aspect of modern biochemistry. The primary target audience for the book includes students, researchers, biologists, chemists, chemical engineers and professionals who are interested in biochemistry, molecular biology and associated areas. The book is written by international scientists with expertise in protein biochemistry, enzymology, molecular biology and genetics many of which are active in biochemical and biomedical research. We hope that the book will enhance the knowledge of scientists in the complexities of some biochemical approaches; it will stimulate both professionals and students to dedicate part of their future research in understanding relevant mechanisms and applications of biochemistry.

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