Clinical Cancer Research

Molecular Pathways: Targeting Cellular Energy Metabolism in Cancer via Inhibition of SLC2A1 and LDHA

Aik T. Ooi[1] and Brigitte N. Gomperts[1,2,3,4]

Abstract

Reprogramming of cellular energy metabolism is widely accepted to be one of the main hallmarks of cancer. The aberrant expression pattern of key regulators in the glycolysis pathway in cancer cells corroborates with the hypothesis that most cancer cells utilize aerobic glycolysis as their main ATP production method instead of mitochondrial oxidative phosphorylation. Overexpression of SLC2A1 and LDHA, both important regulators of the glycolysis pathway, was detected in the premalignant lesions and tumors of lung cancer patients, suggesting the involvement of these proteins in early carcino-genesis and tumor progression in cancer. Preclinical studies demonstrated that inhibiting SLC2A1 or LDHA led to diminished tumor growth *in vitro* and *in vivo*. SLC2A1 and LDHA inhibitors, when administered in combination with other chemotherapeutic agents, showed synergistic antitumor effects by resensitizing chemoresistant cancer cells to the chemotherapies. These results indicate that disrupting SLC2A1, LDHA, or other regulators in cancer cell energetics is a very promising approach for new targeted therapies. *Clin Cancer Res; 21(11); 2440–4. ©2015 AACR.*

Background

Dependence of cancer cells on aerobic glycolysis

Cancer cells alter their primary energy metabolism pathways to support their accelerated rate of growth and proliferation (1). The reprogramming of energy production in cancer cells allows them to generate energy through aerobic glycolysis in the cytoplasm, as opposed to the preferred method of energy production in normal cells via oxidative phosphorylation in the mitochondria (2). The reasons why cancer cells primarily adopt glycolysis as their main method of energy production remains to be fully understood, but one possibility is that aerobic glycolysis provides the tumor cells with glycolytic intermediates that are required for sustained rapid growth (3). This change of cellular energetics also requires an increased uptake of glucose to compensate for the much less efficient ATP production rate by glycolysis compared with mitochondrial oxidative phosphorylation (4–6). This alternative energy metabolism strategy used by tumor cells makes it a potential targetable pathway for cancer therapy.

SLC2A1 and LDHA expression is induced in the early stage of stepwise carcinogenesis

A key protein in the cellular energy metabolism pathway is solute carrier family 2 facilitated glucose transporter member 1 (SLC2A1), also known as glucose transporter 1 (GLUT1; Fig. 1). The main function of SLC2A1 is to supply the cell with glucose by facilitated diffusion of glucose molecules across the plasma membrane when the cellular glucose concentration is low (7). Considering glucose uptake is the first rate-limiting step in aerobic glycolysis, SLC2A1 is often found to be overexpressed in various cancer types, including oral, liver, lung, breast, and endometrial cancer, due to the higher demand of glucose (8–11). In lung cancer, SLC2A1 expression is upregulated at both the RNA and protein levels in premalignant lesions of lung squamous cell carcinoma, when compared with normal lung epithelial basal cells from the same patients (12). In the same study, the expression of SLC2A1 was found to further increase when the premalignant lesions progressed to invasive carcinomas. These observations suggest that SLC2A1 plays a very important role in the initiation and progression of tumor, and could be one of the driver genes in lung cancer and possibly other cancers too.

Although increasing glucose transport could be considered as the first rate-limiting step in allowing lung carcinomas to utilize aerobic glycolysis, many other factors are involved in maintaining this reprogramming of cellular energetics. Upon being transported from the plasma membrane into the cell, glucose molecules go through glycolysis to produce ATP and pyruvate. Under normal conditions, pyruvate enters the mitochondria and goes through the tricarboxylic acid (TCA) cycle for highly efficient ATP production (Fig. 1). In cancer cells, pyruvate is rapidly converted to lactate, and thus prevented from entering the mitochondria for the TCA cycle, thereby allowing the cells to continually rely on aerobic glycolysis. The conversion of pyruvate to lactate is catalyzed by the enzyme lactate dehydrogenase A (LDHA; Fig. 1). LDHA has been shown to be overexpressed in many types of cancer, including lung cancer, breast cancer, and pancreatic cancer (13–15). Like SLC2A1, transcription of *LDHA* is induced in a stepwise manner from normal epithelial basal cells to premalignant lesions, and again from premalignant lesions to carcinomas

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Figure 1.
Cellular energy metabolism pathways in cancer. Green molecules represent upregulated or activated proteins in cancer; red molecules represent downregulated or inhibited proteins in cancer. Glucose molecules enter the cell via facilitated diffusion by SLC2A1. HK2, GAPDH, and other glycolytic enzymes convert glucose to pyruvate and ATP through glycolysis. Pyruvate could either enter the mitochondria or be converted to lactate by LDHA, a process that also regenerates NAD^+ required for glycolysis. Pyruvate that enters the mitochondrion is converted to acetyl-CoA by PDH before entering the TCA cycle. PDK1 inhibits PDH and reduces the formation of TCA cycle starting material. Increased mitochondrial energy production also generates ROS that at high levels could cause oxidative stress and subsequent apoptosis. An elevated level of LDHA is associated with reduced mitochondrial ROS production. LDHA is induced by HIF1A, which also increases the expression of PDK1 and HK2. MYC activates the expression of HIF1A, GAPDH, and SLC2A1, driving the cell to utilize aerobic glycolysis instead of mitochondrial oxidative phosphorylation. Finally, inhibition of MYC, HIF1A, and SLC2A1 by functional TP53 in a healthy cell reverses the oncogenic effects caused by overexpression of these proteins.
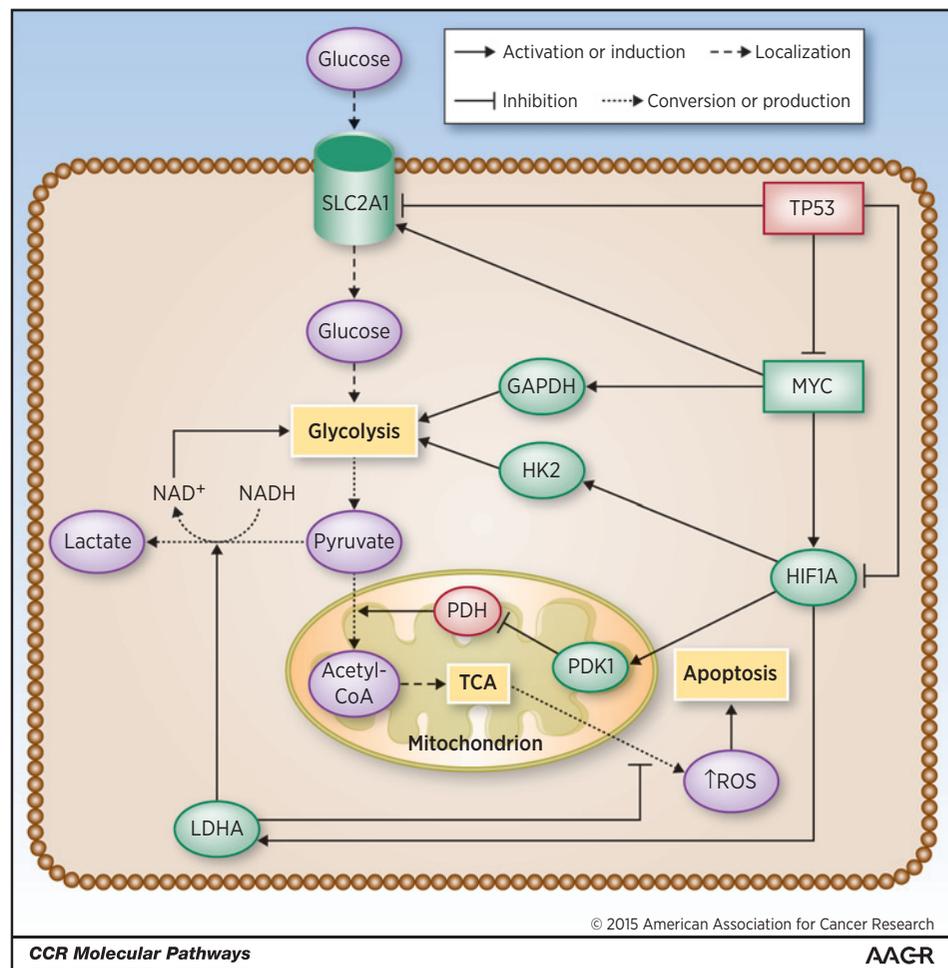
in lung cancer patients (12, 16). The conversion of pyruvate to lactate by LDHA also generates NAD^+ from NADH, thus replenishing the cell with the NAD^+ required for glycolysis.

Other key regulators of aerobic glycolysis in cancer

LDHA is transcriptionally activated by hypoxia-inducible factor 1 alpha (HIF1A), a proglycolysis protein that also activates other genes of glycolytic enzymes such as hexokinase 2 (HK2; refs. 17, 18). HK2 is an enzyme responsible for the phosphorylation of glucose to form glucose-6-phosphate in the first step of glycolysis, and is found to be overexpressed in both premalignant lesions and tumors of lung cancer patients (12). *HIF1A* expression is induced in lung cancer, colorectal carcinoma, and other cancers, and is considered to be oncogenic, partly due to its role in activating proglycolytic genes, and thus enabling aerobic glycolysis (12, 16, 17). HIF1A also indirectly prevents glycolytic products from entering the TCA cycle via the activation of pyruvate dehydrogenase kinase 1 (PDK1), which is an inhibitor of pyruvate dehydrogenase (PDH; ref. 19). Pyruvate that enters the mitochondria is first converted to acetyl-CoA by PDH before entering the TCA cycle. Inhibition of PDH ensures that the starting molecule for the TCA cycle is never made.

MYC is generally considered to be a "master regulator" of cell growth and metabolism. Many aberrantly expressed genes in cancer are known transcriptional targets of MYC (20). On the basis of the changes in gene-expression profiles during stepwise lung carcinogenesis, it is predicted that MYC activity is increased during the early stages as premalignant lesions are forming (12). Immunofluorescent staining also revealed that MYC remains in the cytoplasm of normal lung epithelial basal cells, but localizes to the nuclei of cells in premalignant lesions and invasive carcinomas of lung cancer patients, implying the involvement of MYC in the initiation and early progression of tumor. Although the oncogenic effects of MYC are often attributed to its pro-proliferative properties, MYC is involved in promoting the reprogramming of cellular energetics in cancer cells, as it is known to activate the transcription of *HIF1A*, as well as stabilizing the HIF1A protein (21). MYC also induces the transcription of *SLC2A1* and GAPDH (an enzyme that catalyzes the conversion of glyceraldehyde 3-phosphate to D-glycerate 1,3-bisphosphate during the sixth step of glycolysis; ref. 22). *GAPDH* expression is upregulated in numerous types of cancer, including lung cancer, colorectal carcinoma, and breast cancer (12, 23, 24).

Another key regulator of energy metabolism is the tumor protein p53 (TP53), a well-recognized tumor suppressor. Although TP53 is involved in a wide spectrum of cellular functions, it also plays an important role in preventing the cell from reprogramming its energetic metabolic pathway. TP53

inhibits the expression of *SLC2A1*, *HIF1A*, and *MYC*, and also promotes the degradation of HIF1A (25, 26). Therefore, functional wild-type TP53 would reverse the effects of the pro-glycolytic events required for cancer progression. It has been known that the TP53 gene is often mutated in cancer patients (27). Alterations of TP53 target gene-expression patterns in tissue samples of lung cancer patients further predict a loss of function in TP53 during carcinogenesis (12). On the basis of these observations, it appears that the switch to dependence on aerobic glycolysis by cancer cells as the primary energy-producing pathway is important in the biology of carcinogenesis, and therefore makes this pathway an ideal target to develop cancer therapies.

Clinical–Translational Advances

Targeting SLC2A1

Most therapeutic strategies that are being developed to target the cellular energetic metabolism pathways in cancer are in the preclinical phase of drug development. Because SLC2A1 enables the cellular transport of glucose, which is the first rate-limiting step of glucose metabolism, it makes the most sense to inhibit glycolysis by perturbing the function of SLC2A1. WZB117 is a small-molecule inhibitor of SLC2A1, and its feasibility and outcome in repressing the activity of SLC2A1 have been extensively tested *in vitro* and *in vivo* (28). When treated with WZB117, A549 lung cancer cells showed a rapid and complete inhibition of glucose transport starting 1 minute after treatment. WZB117 also significantly inhibited the proliferation of A549 cells by 50% ($P \leq 0.001$) 48 hours after treatment when compared with the effect observed in the NL20 noncancerous lung cell line. Blocking glucose transport with WZB117 treatment in A549 cells reduced the rate of glycolysis and the levels of cyclins and phosphorylated retinoblastoma protein (RB1) within 6 hours. Cell-cycle arrest and senescence were observed within 24 hours, which eventually led to necrosis within 48 hours (28). When tested *in vivo* using a human tumor xenograft model with s.c. injection of A549 cells into nude mice, treatment with WZB117 for 10 weeks reduced the tumor growth by 70% ($P < 0.05$) when compared with grafts from mock-treated mice.

Another strategy being tested to target SLC2A1 is by RNAi using shRNA. When tested on mouse mammary tumor cell lines, shRNA targeting *SLC2A1* decreased glucose transport and consumption, reduced lactate secretion, and inhibited growth of the tumor cells on plastic as well as in soft agar gel ($P < 0.05$; ref. 29). When tested *in vivo* by injecting the *SLC2A1* shRNA-treated tumor cells into the mammary glands of athymic nude mice, growth inhibition of the treated tumor cells was observed 8 days after implantation when compared with cells treated with control shRNA ($P < 0.05$). Eliminating *SLC2A1* expression in transformed mammary epithelial cells by a Cre-Lox system resulted in 35% reduction of tumor size when injected into contralateral mammary glands of athymic nude mice, compared with the tumors formed by control cells after 20 days ($P < 0.05$; ref. 29).

In addition to testing SLC2A1 inhibitor alone as a targeted therapy, efforts are also in progress to evaluate SLC2A1 inhibition in combination with other cancer therapeutics. When administered *in vitro* along with the anticancer drug cisplatin or paclitaxel in lung cancer cell lines A549 and H1229 and breast cancer MCF7 cells, WZB117 showed synergistic antitumor effects with each of these drugs by inhibiting the growth of the cells to a greater extent than when they were tested alone (28). In a different study, phloretin, a natural inhibitor of SLC2A1, showed a synergistic antitumor effect when administered in combination with daunorubicin. Phloretin inhibited over 60% of glucose uptake and improved the anticancer efficiency of daunorubicin more than 2-fold by reducing the hypoxia-enabled drug resistance in SW260 ($P < 0.001$) and K562 ($P = 0.012$) cells (30). A third study showed that inhibiting SLC2A1 *in vitro* with targeted antibody or shRNA sensitized Cal27 head and neck carcinoma cells to cisplatin treatment under both normoxic and hypoxic conditions (31). Although these results show promising effects of SLC2A1 inhibition in combination with other anticancer drugs, more elaborate studies are needed to identify the mechanism for the synergistic antitumor activity in the combined therapies.

Targeting LDHA

A complete loss of LDHA protein in humans due to hereditary partial deletion of the *LDHA* gene only results in non–life-threatening and relatively mild cases of exertional myoglobinuria (32). This observation proves that LDHA is a safe therapeutic target for cancer patients with an increased level of LDHA expression. In A549 lung cancer cells, *in vitro* knockdown of *LDHA* by shRNA resulted in apoptosis, potentially mediated by reactive oxygen species (ROS) produced via enhanced oxidative phosphorylation in the mitochondria (33, 34). In KRAS- and EGFR-driven lung cancer transgenic mouse models, conditional inactivation of *LDHA* resulted in the formation of significantly smaller tumors ($P < 0.05$), as well as a more than 50% reduction in tumor area in established tumors ($P < 0.01$; ref. 35). These results suggest that LDHA inhibition reduces carcinogenesis and leads to tumor regression.

In vitro treatment of FX11 (3-dihydroxy-6-methyl-7-(phenyl-methyl)-4-propylnaphthalene-1-carboxylic acid), a specific LDHA inhibitor, resulted in elevated oxygen intake, ROS generation, oxidative stress, and apoptosis in P493 human lymphoma B cells (36). The results of further tests in the same study also suggest that FX11 modifies cellular energy metabolism via inhibition of glycolysis, thereby targeting cells that are dependent on glycolysis. FX11 also inhibits the xenograft growth of P493 lymphoma B cells and P198 human pancreatic cancer cells in mice, showing *in vivo* efficiency. More recently, galloflavin and N-hydroxyindole–based molecules have been discovered to inhibit LDHA (37, 38). Although early results show feasibility with these antitumor agents, more studies are needed to investigate their effectiveness.

As in the case with SLC2A1 inhibitors, the efficacy of combining LDHA inhibition with other chemotherapies has been evaluated. An *in vitro* study with paclitaxel-resistant breast cancer cells demonstrated that LDHA inactivation by siRNA or by another LDHA inhibitor, oxamate, significantly increased the sensitivity of the cells to paclitaxel treatment, resulting in 2- to 10-fold growth inhibition ($P < 0.01$; ref. 39). LDHA inhibition by oxamate also significantly enhanced the therapeutic effects of trastuzumab in treating ERBB2-positive trastuzumab-resistant breast cancer cells *in vitro* and *in vivo* ($P < 0.01$; ref. 40). Treatment with FX11 in combination with FK866, which inhibits the synthesis of NAD^+, resulted in significant tumor regression of lymphoma xenografts (36). Finally, inhibition of LDHA by shRNA sensitized A549 lung cancer cells to low doses of paclitaxel, leading to higher rates of apoptosis (33).

Concluding Remarks

Preclinical data suggest that SLC2A1 and LDHA are both viable drug targets for cancer therapy. Inactivating SLC2A1 or LDHA affects the glycolytic pathway in cancer cells, and eventually causes apoptosis *in vitro* and *in vivo*. With SLC2A1 inhibition, the antitumor effect is due to glucose starvation that ultimately leads to cell death. The cancer cytotoxicity effect observed in LDHA inhibition is a result of increased oxidative phosphorylation in the mitochondria, which causes oxidative stress from elevated ROS production. Although the data are very promising, inhibitors for both SLC2A1 and LDHA are only in the preclinical stages of drug development, and extensive clinical trials are needed to fully evaluate their effectiveness. In addition to SLC2A1 and LDHA, several other potential cancer therapies target the cellular energetic metabolism pathway in tumor. Among them are prospective inhibitors for GAPDH, HK2, and PDK1 (41–46). Preclinical data for these inhibitors are encouraging; therefore, they represent additional options for targeting the enhanced aerobic glycolysis in cancer.

Regrettably, therapies designed to target this pathway have not been fully translated to the clinic. One of the major hurdles to the success of these therapies is the potential systemic toxicity, a very common adverse effect found with all antitumor drugs. However, advancements in imaging technology have made it possible for localized delivery of drugs to the tumor, which essentially eliminates systemic toxicity while enhancing the potency of the drugs (47). This image-assisted drug delivery technology is still a very novel approach. With further development of this process, precise delivery of SLC2A1 or LDHA inhibitors to the tumors, either as independent therapies, adjuvant, or neoadjuvant therapies, or in combination with other antitumor agents, is a highly feasible approach in treating cancer patients.

Disclosure of Potential Conflicts of Interest

A.T. Ooi is an employee of Fluidigm. No potential conflicts of interest were disclosed by the other author.

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