World Journal of Biological Chemistry

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DOI: 10.4331/wjbc.v6.i3.148

World J Biol Chem 2015 August 26; 6(3): 148-161
ISSN 1949-8454 (online)

REVIEW

Metabolic interplay between glycolysis and mitochondrial oxidation: The reverse Warburg effect and its therapeutic implication

Minjong Lee, Jung-Hwan Yoon

Minjong Lee, Jung-Hwan Yoon, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul 110-799, South Korea

Author contributions: Lee M and Yoon JH conceived and wrote this review.

Supported by Grant to Dr. Jung-Hwan Yoon; the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, No. 20100007381; and by the Liver Research Foundation of Korea.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Correspondence to: Jung-Hwan Yoon, MD, PhD, Professor, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, South Korea. yoonjh@snu.ac.kr
Telephone: +82-2-20722228
Fax: +82-2-7436701

Received: April 19, 2015
Peer-review started: April 21, 2015
First decision: May 13, 2015
Revised: May 26, 2015
Accepted: July 21, 2015
Article in press: July 23, 2015
Published online: August 26, 2015

Abstract

Aerobic glycolysis, *i.e.*, the Warburg effect, may contribute to the aggressive phenotype of hepatocellular carcinoma. However, increasing evidence highlights the limitations of the Warburg effect, such as high mitochondrial respiration and low glycolysis rates in cancer cells. To explain such contradictory phenomena with regard to the Warburg effect, a metabolic interplay between glycolytic and oxidative cells was proposed, *i.e.*, the "reverse Warburg effect". Aerobic glycolysis may also occur in the stromal compartment that surrounds the tumor; thus, the stromal cells feed the cancer cells with lactate and this interaction prevents the creation of an acidic condition in the tumor microenvironment. This concept provides great heterogeneity in tumors, which makes the disease difficult to cure using a single agent. Understanding metabolic flexibility by lactate shuttles offers new perspectives to develop treatments that target the hypoxic tumor microenvironment and overcome the limitations of glycolytic inhibitors.

Key words: Hepatocellular carcinoma; Oxidative stress; Metabolic interventions; Aerobic glycolysis; Lactate

Core tip: The Warburg effect plays a vital role in cancer cell proliferation and survival, and contributes to the initiation of tumor metastasis. To adapt to rapidly changing microenvironment for survival such as from normoxia to hypoxia, cancer cells vary in metabolic phenotype; "metabolic flexibility". Even in a hypoxic condition, oxidative cancer cells and/or stromal cells should theoretically exist to support the metabolic fuel for glycolytic cancer cells and handle lactate *via*

the dynamic shuttle; "the reverse Warburg effect". Treatments against tumor metabolism may aim to target two distinct metabolic pathways of glycolysis and mitochondrial oxidative phosphorylation.

Lee M, Yoon JH. Metabolic interplay between glycolysis and mitochondrial oxidation: The reverse Warburg effect and its therapeutic implication. *World J Biol Chem* 2015; 6(3): 148-161 Available from: URL: http://www.wjgnet.com/1949-8454/full/v6/i3/148.htm DOI: http://dx.doi.org/10.4331/wjbc.v6.i3.148

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third cause of cancer-related mortality all over the world[1]. Despite the recent development of various types of targeted agents, minimal improvements have been identified in the survival of patients with advanced HCC since the introduction of sorafenib 10 years ago[2]. To overcome the limitations of current anticancer agents, new strategies must be developed.

Most previous studies have strongly suggested the metabolic reprogramming of cancer cells into aerobic glycolysis, *i.e.,* the Warburg effect, in the process of carcinogenesis and adjustment for the hypoxic tumor microenvironment. Based on this concept, the development of anticancer agents that target the enzymes involved in glycolysis appears to be promising. 3-bromopyruvate (3-BP), is a potent anticancer agent that inhibits the glycolytic pathway primarily leads to a depletion of energy reserves. Previous studies have demonstrated that 3-BP could have strong anticancer effects in various cancer types. However, in a case study performed in Egypt, the killing effect of 3-BP was not as potent as expected in the treatment of a 28-year-old man who presented with stage Ⅳ metastatic melanoma. The patient died of cancer progression even though he had received 3-BP treatment[3].

Based on the cancer progression despite 3-BP treatment in this case, mechanisms beyond the Warburg effect may contribute to cancer cell survival, *i.e.,* evading the glycolytic pathway or attenuating the 3-BP anticancer effect. One potential explanation of the mechanism is that cancer cells might have a preference to produce energy reserves *via* mitochondrial oxidative phosphorylation (OXPHOS) rather than high glycolysis according to their surrounding conditions. The cells use lactate from tumor stromal cells, which is the end product of glycolysis and can fuel mitochondrial OXPHOS after conversion to pyruvate. This phenomenon has been referred to as the "reverse Warburg effect", which indicates increased aerobic glycolysis of stromal cells adjacent to tumor cells[4]. Another potential reason for 3-BP resistance might be the capability of tumor cells to balance the redox potentials, which play a key role in drug detoxification and cellular protection from oxidative injury by free radicals and peroxides, *i.e.,* "chemoresistance" to 3-BP[5].

In this review, we describe the clinical implication of the Warburg effect with a high redox potential, and the roles of mitochondrial OXPHOS with a focus on lactate shuttles beyond the Warburg effect. Given the importance as modulators of tumor cell metabolism, these approaches may represent promising therapeutic targets to potentiate the anticancer effect of 3-BP, which has been well-known as the strongest inhibitor of glycolysis in cancer.

WARBURG EFFECT: CURRENT CLINICAL IMPLICATIONS IN CANCER

Warburg first reported an anomalous characteristic of energy metabolism in cancer cells[6,7], even in the presence of oxygen, cancer cells can accelerate glycolysis rather than mitochondrial OXPHOS; "aerobic glycolysis". Aerobic glycolysis is seemingly contradictory phenomena because cancer cells must compensate for the 18-fold lower efficiency of ATP production afforded by glycolysis as compared to mitochondrial OXPHOS. To compensate this lower efficiency, the cells upregulate glucose transporters such as GLUT1[8-10]. This inefficient energy metabolism provides cancer cells with several advantages: (1) balancing the redox potential inner cell; and (2) increased biosynthesis of intermediate macromolecules, anti-apoptosis, and efficient signaling through metabolites as compared with mitochondrial OXPHOS[9].

In hypoxic tumor cells, the overexpression of glucose transporters and glycolytic enzymes such as hexokinase Ⅱ (HK Ⅱ), phosphofructokinase (PFK), phosphoglycerate kinase, and lactate dehydrogenase (LDH), has been investigated[11]. It was reported that high serum levels of glucose transporter (GLUT) 1, GLUT 3, aldolase-B, and HK Ⅱ have been significantly associated with poor prognosis in various types of malignancies[12]. Among them, HK Ⅱ, involved in the first rate-limiting step of glycolysis, has been related to anti-apoptosis. A predominant fraction of HK Ⅱ was bound to the voltage-dependent anion channel (VDAC) at the outer membrane of the mitochondria. Among the proposed mechanism of chemoresistance in cancer cells was the decreased availability of free VDAC sites that interact with pro-apoptotic proteins (Bax). HK Ⅱ binds to the VDAC site and this interaction prevents the activation of Bax[13]. In other words, HK Ⅱ play a key role for prevention of chemotherapy-induced, mitochondria-mediated, tumor cell apoptosis. In addition, this glycolysis pathway can be further accentuated under the hypoxic conditions in many tumors: the hypoxic condition can upregulate glucose transporters and induce multiple enzymes of the

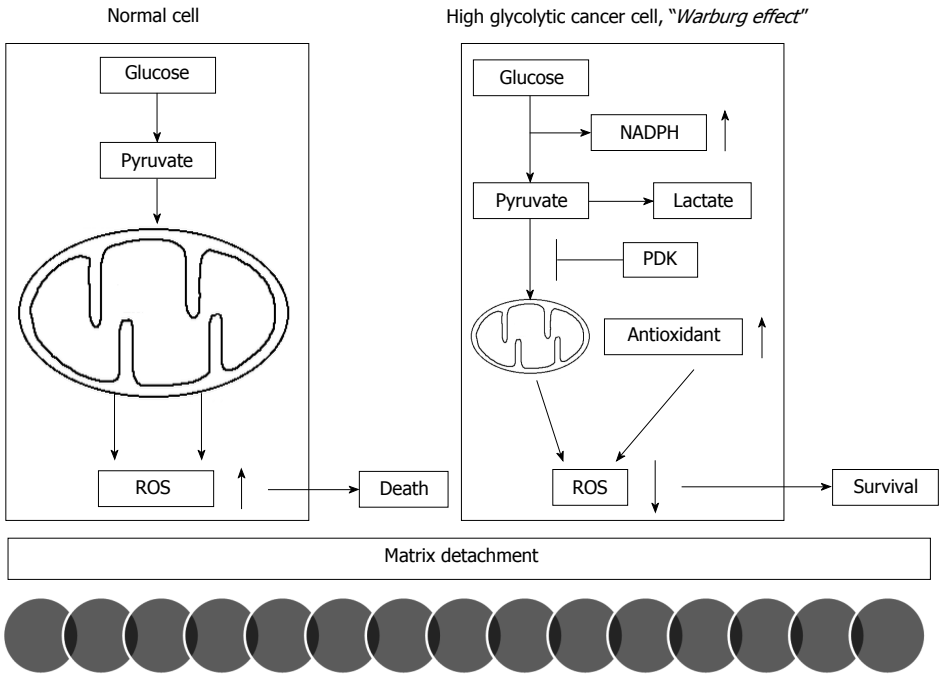

Figure 1 The Warburg effect contributes to the initiation of tumor metastasis by lowering intracellular reactive oxygen species levels. After matrix detachment, cancer cells decrease intracellular ROS levels through inducing enzymes involved in the glycolysis and antioxidant systems for their survival. The Warburg effect is strongly linked with modulation of ROS system. PDK: Pyruvate dehydrogenase kinase; ROS: Reactive oxygen species.

glycolytic pathway[10,14,15]. For example, both Ras oncoprotein and hypoxia can independently increase HIF1a and HIF2a transcription factor levels which upregulate glycolysis[14,16,17]. Our group demonstrated that hypoxia stimulates HCC cellular growth through hexokinase Ⅱ induction, which thereby may participate in HCC progression, and the blockage of this enzyme may be therapeutically efficacious in human HCCs[18,19]. Although tumor cells can redirect energy metabolism of "aerobic glycolysis", it has become apparent that oxygenation, which ranges from normoxia to hypoxia, is not always static in tumor microenvironment, but instead dynamically fluctuates as a result of the dynamic changes of the tumor-associated neovasculature[20].

WARBURG EFFECT WITH ROS: INITIATION OF METASTASIS

The acceleration of glycolysis in cancer cell energy metabolism could reduce the production of reactive oxygen species (ROS) by less reliance on mitochondrial OXPHOS and simultaneously enhance the redox potential *via* an increase in NADPH in the pentose phosphate pathway as byproducts for biosynthetic pathways of proliferation. This contribution of the Warburg effect to the balance of redox potential plays a pivotal role in the initiation of metastasis; matrix detachment. While normal cells attenuate mitochondrial OXPHOS in response to matrix detachment for their survival, many cancer cells already limit mitochondrial OXPHOS before detachment because of the Warburg effect. Normal cells activate PDK4 to inhibit PDH following detachment to upregulate glycolytic pathway. However, cancer cells already express high levels of PDK1 under attached conditions[21]. PDK1 and PDK3 expression in various cancers significantly correlates with patients' prognosis: tumor histological grades and disease-free survival[22,23]. PDK inhibition or PDH activation in cancer cells stimulates mitochondrial OXPHOS and thereby increase ROS production. Excess production of intracellular ROS levels increase their susceptibility to cell death after matrix detachment, which leads to a decreased metastatic potential[21]. Therefore, the Warburg effect allows cancer cells to evade cellular oxidative stress that would be produced by mitochondrial OXPHOS for glucose metabolism[24]. Thus, the reduction of ROS levels, which promotes metastasis, may represent an advantage given by the Warburg effect (Figure 1). Increased glucose consumption diverts more glucose carbon into the oxidative branch of the pentose phosphate pathway, which represents a major source to generate NADPH[25]. NADPH is a critical cofactor for the replenishment of reduced glutathione (GSH) in a cell. Cancer cells can further enhance this antioxidant generation pathway *via* PKM inhibition when oxidative stress increases[26].

In addition to the Warburg effect, cancer cells also potentiate antioxidant systems to cope with increased oxidative stress[25]. For example, while MnSOD is induced following matrix detachment in normal cells[27], MnSOD is constitutively overexpressed in cancer cells. Furthermore, increased MnSOD expression in cancer is significantly associated with poor prognosis[27-29]. An enhanced antioxidant capacity allows cancer cells to

better survive detachment-induced oxidative stress and initiate to metastasize. In a lung cancer mouse model, antioxidant treatments have consistently reduced oxidative stress and accelerated lung cancer progression[30].

LIMITATIONS OF THE WARBURG EFFECT AND GLYCOLYTIC INHIBITORS

To adapt to rapidly changing microenvironment for their survival such as from normoxia to hypoxia[31,32], each cancer cells may vary in metabolic phenotype even in a single tumor mass; "metabolic flexibility"[33]. Because total ATP production *via* the glycolytic pathway does not generally exceed 50%-60%[34], mitochondrial OXPHOS still, to a certain extent, contributes to ATP generation in cancer cells, *i.e.,* a mixture of glycolysis and mitochondrial OXPHOS[35]. The ratio of contribution to ATP production in cancer cells can be rapidly changed to maintain pace with the alteration of the tumor microenvironment. Herst *et al*[36] reported that energy production for tumor cell growth was altered from mitochondrial OXPHOS to accelerated glycolysis according to changes from normoxia to hypoxia: mitochondrial OXPHOS contributes to total ATP production, which was 91% in normoxia and reduced to 36% in hypoxia.

Given this flexibility, all cancer cells did not completely depend on accelerated glycolysis. Previous studies reported that mitochondrial OXPHOS in many cancers can be well-functioned to produce ATPs[9,37-40]. These authors have concluded that the Warburg effect is a result of accelerated glycolysis which suppressed mitochondrial OXPHOS rather than the initial impairments in mitochondrial OXPHOS. If glycolysis is suppressed in cancer cells, the mitochondrial OXPHOS function can be recovered[35,39,41,42]. In a noticeable investigation, Fantin *et al*[39] demonstrated that when glycolysis was inhibited by suppression of LDH-A in cancer cells, mitochondrial OXPHOS could be restored to compensate for energy production. This study reported that both LDH-A and mitochondrial function were modulated by the metabolite level such as pyruvate and the NADH/NAD+ ratio. This result indicates that cancer cells have the capacity of regulating ATP production by mitochondrial OXPHOS to adapt to the rapidly changing microenvironment.

According to a proposal by Smolková *et al*[41], metabolic phenotypes in cancer cells can be simply divided into two subgroups with each condition of the tumor microenvironment: (1) enhanced glycolysis and suppressed mitochondrial OXPHOS with a hypoxic condition; and (2) relatively suppressed glycolysis and restoration of mitochondrial OXPHOS with nutrient shortage because of high proliferation rates. This proposal explained that the Warburg phenotype is not a universal finding, and mitochondrial respiration impairment is not a fixed feature of cancer cells[41].

Although the glycolytic inhibitors targeting the Warburg effect have been investigated in various cancer types, the glycolytic inhibitors with the exception of 3-BP (a lactate analog)[18,19,43-70], 3-BrOP (a 3-bromopyruvate derivative)[71-74], and dichloroacetate (DCA)[75-98] have demonstrated low efficacy in arresting tumor growth when used alone[99]; these inhibitors include 2-deoxy-D-glucose (a glucose analog)[70,100-112], lonidamine (a derivative of indazole-3-carboxylic acid)[113-132], methyl jasmonate on HK[133-161], 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one on PFK[162-166], and iodoacetate on glyceraldehydes-3-phosphate dehydrogenase (GAPDH)[167-170].

Among various glycolytic inhibitors, 3-BP could only target two energy pathways of glycolysis and mitochondrial OXPHOS. The mechanism for 3-BP action suggested that mitochondrial HK Ⅱ is essential for the high glycolytic capacity *via* the utilization of mitochondrial ATP rather than cytosolic ATP, and the lowering of mitochondrial OXPHOS capacity by limiting Pi and ADP delivery to the mitochondria[171,172]. In contrast, DCA would affect only in cancer cells having impaired mitochondria function by PDK inhibition: otherwise alternative energy sources could compensate for the inhibited glycolysis through the competent mitochondria[173]. No phase Ⅲ randomized clinical trial of glycolytic inhibitors has exhibited satisfactory clinical outcomes[174].

Of note, the previously described studies that have reported the anticancer effects of these glycolytic inhibitors, with the exception of 3-BP, have exhibited common characteristics: (1) a low efficacy for anticancer effects when used alone; (2) capable of sensitizing cancer cells to conventional chemotherapy drugs, such as 5-fluorouracil, cisplatin, doxorubicin, and sorafenib; (3) the role of a sensitizer to make cancer cells vulnerable to radiotherapy and photodynamic therapy; and (4) an increase in the intracellular ROS levels as an important mechanism to induce their apoptosis.

PARADIGM SHIFT FROM THE WARBURG EFFECT TO THE REVERSE WARBURG EFFECT BASED ON LACTATE SHUTTLE

To explain metabolic flexibility, *i.e.,* mitochondrial OXPHOS, the reverse Warburg effect was suggested[175]; cancer cells educate carcinoma-associated fibroblasts (CAFs) to enhance aerobic glycolysis, and CAFs thereby produce lactate, which was converted to pyruvate and utilized for mitochondrial OXPHOS in cancer cells[175,176]. Tumor cells and CAFs influence each other in energy metabolites for co-evolution in cancer progression. A growing body of evidence indicates that lactate as an end product of glycolysis in hypoxic cancer cells and/or CAFs is not a waste product. Lactate can be used as

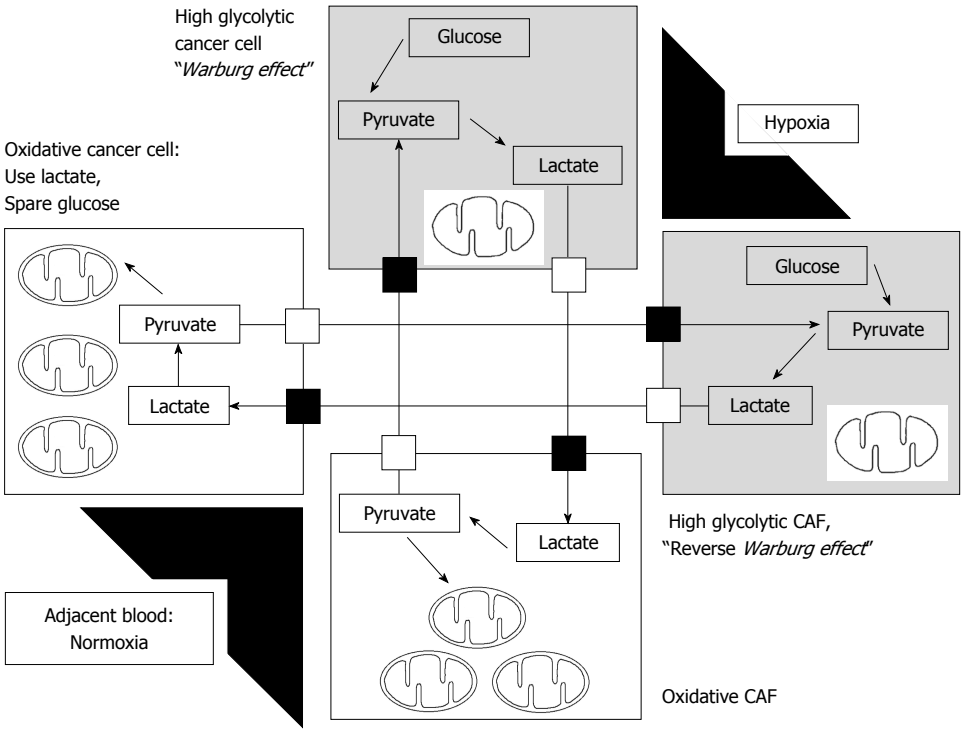

Figure 2 Metabolic interplay between high glycolytic cells and mitochondrial OXPHOS cells *via* lactate shuttle: the black box indicates monocarboxylate transporter 1, and the white box indicates monocarboxylate transporter 4: The gray zone means the hypoxic condition. Through MCT1 and 4, energy metabolites such pyruvate and lactate go in and out between glycolytic and oxidative cells: two roles of energy fuel and maintenance for acid-base balance in tumor microenvironment. MCT: Monocarboxylate transporters; CAF: Carcinoma associated fibroblast.

energy fuel for oxygenated tumor cells and/or oxidative CAFs as shown in Figure 2. Lactate is converted to pyruvate by LDH-B, which can enter the mitochondria to produce ATP in the cells with restored mitochondrial OXPHOS[31,40,176-181]. Particularly, oxidative tumor cells in normoxic microenvironment use mitochondrial OXPHOS to spare glucose, which can be utilized by glycolytic tumor cells located in hypoxic microenvironment.

During communication between glycolytic and oxidative cells, MCT1 and MCT4 are key players in this metabolic cross-talk. Influx of lactate by oxidative cancer cells occurs through MCT1, whereas lactate is released through MCT4[177]. MCT1 inhibition can make a metabolic shift from mitochondrial oxidation to glycolysis, which thereby induce glucose consumption. MCT4 inhibition can directly induce cell death *via* accumulation of intracellular lactic acid in hypoxic tumor cells[177]. Clinical phase I trials investigating MCT1 inhibitors are ongoing (http://clinicaltrials.gov/show/NCT01791595).

In addition to metabolic fuel by lactate shuttle, this phenomenon can maintain an acid-base balance *via* the prevention of the development of a fatal acidic environment in cancer cells[181,182]. Koukourakis *et al*[181,182] reported that increased expression of MCT1, LDH, and PDH in CAFs metabolically utilize lactate produced by tumor cells. In the other way, previous studies reported that some CAFs can undergo aerobic glycolysis and provide nearby oxidative cancer cells with the released lactate[176,182,183] (Figure 2).

Furthermore, accumulation of lactic acid, which represents high glycolysis rates in hypoxic conditions, reflects poor vascularity caused by rapid tumor growth. Previous studies demonstrated that lactate released from glycolytic tumor cells through MCT4 can stimulate angiogenesis and tumor growth *via* IL-8 dependent pathway[184]. Taken together, these findings establish important roles for lactate shuttles in tumors: (1) it acts as both a metabolic fuel; and (2) maintains an acid-base balance in cancer cells; and (3) signals for angiogenesis in hypoxic microenvironment. Finally, cancer cells can adapt to rapid changes in the tumor microenvironment through the metabolic interplay between oxidative and glycolytic cells, such as glycolytic and oxidative tumor cells and glycolytic and oxidative stromal cells, through lactate shuttle: "tumor heterogeneity and metabolic flexibility" (Figure 2).

THERAPEUTIC IMPLICATIONS OF TARGETING THE METABOLIC INTERACTION BETWEEN HIGH GLYCOLYTIC CELLS AND MITOCHONDRIAL OXPHOS CELLS

Although increasing evidence has recently indicated that mitochondrial OXPHOS and lactate shuttle may

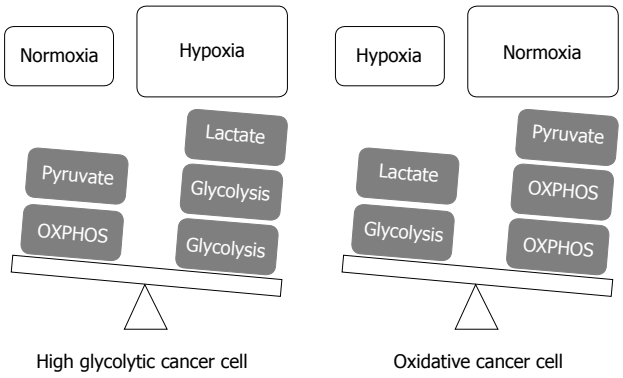

Figure 3 Metabolic flexibility of cancer cells depends on the tumor microenvironment: metabolic changes according to oxygen gradients. In hypoxic condition, glycolysis mainly contributes to produce ATPs with lowering reactive oxygen species production, thereby closely links with initiation of metastasis. In normoxic condition, mitochondrial oxidation more contributes for energy production than glycolysis. For survival, cancer cells adjust to dynamic changes between hypoxia and normoxia in tumor microenvironment. OXPHOS: Oxidative phosphorylation.

contribute to cancer cell survival and progression, the Warburg effect still plays a pivotal role in cancer cell metabolism and the initiation of metastasis in hypoxic conditions as previously discussed. Therefore, therapeutic strategies should focus on both targets, glycolysis and mitochondrial OXPHOS. Even though some studies reported that mitochondrial OXPHOS is also one of 3-BP targets[185], 3-BP has been mainly demonstrated to be the most potent glycolytic inhibitor among various types of inhibitors. However, including our studies, the results of *in vivo* studies that have used human HCC cell lines did not exhibit complete remission, but showed only partial remission after 3-BP treatment[18,19,43-70]. One reason why 3-BP did not completely suppress tumor growth might be the low efficiency to suppress mitochondrial OXPHOS, the lactate shuttle, and high redox potential in cancer cells. To overcome the weakness of glycolytic inhibitors, the inhibitors to target mitochondrial OXPHOS and other involved mechanisms such as the suppression of ROS production, might be effective when used simultaneously with glycolytic inhibitors as a combination treatment.

The metabolic interplay (lactate shuttle) between glycolytic and oxidative cells in tumors is modulated by two simple compartments for ATP production; glycolytic pathway and mitochondrial OXPHOS. Therefore, a combined treatment targeting both glycolysis and mitochondrial OXPHOS, could potentially be effective in suppression of tumor growth. Although various agents have been introduced to suppress mitochondrial metabolism, two agents, including metformin and glutamate dehydrogenase 1, were noticeable regarding their safety and potency. The metformin is widely used for Type Ⅱ diabetes in practical fields and has anti-cancer effects in animal models. Previous studies demonstrated that metformin inhibits complex Ⅰ *via* the inhibition of ubiquinone reduction and independently stimulates ROS production by the complex Ⅰ flavin[186-188]. It might be more clinically meaningful in terms of tolerable safety for a long period as demonstrated in diabetic patients.

Another promising agent that targets mitochondrial metabolism is the mitochondrial enzyme glutamate dehydrogenase 1 (GDH1). Previous reports demonstrated that glutamine may be utilized as the energy fuel for mitochondrial OXPHOS in cancer cells[189-192]. GDH1 is upregulated in human cancers and important for redox homeostasis by controlling the intracellular levels of its product alpha-ketoglutarate and subsequent metabolite fumarate, which subsequently activates glutathione peroxidase 1, *i.e.,* the antioxidant system. Targeting GDH1 by a small molecule inhibitor, the purpurin analog R162, resulted in an imbalanced redox homeostasis, which led to suppress tumor growth[193].

As described above, the common characteristics of glycolytic inhibitors were to increase ROS levels in cancer cells. Thus, a further increase in ROS stress using exogenous ROS enhancers combined with glycolytic inhibitors might effectively increase ROS levels above the threshold stimulating cell death pathways. The vulnerability for ROS stress in normal and cancer cells is quite different. Normal cells have tolerability for a certain level of exogenous ROS stress because of their high antioxidant capacity for lowering the ROS level and thereby prevent to reach the cell-death threshold[194,195]. In cancer cells, the increased ROS production from metabolic disarrangement and rapid proliferation may induce an upregulation of antioxidant capacity, *i.e.,* vulnerable redox equilibrium with high ROS production and elimination to maintain the ROS levels below the threshold for cell death[196,197]. Thus, cancer cells would be more vulnerable to increased oxidative stress induced by exogenous ROS enhancers that directly or indirectly suppress the antioxidant system[198-201]. These characteristics may provide a biochemical basis for a combination treatment of glycolytic inhibitors and ROS enhancers.

CONCLUSION

There have been a lot of advances to understand the importance of the Warburg effect and the metabolic interplay between glycolytic and oxidative cells in terms of lactate shuttle in previous decades. As previously discussed, the Warburg effect plays a vital role in cancer cell proliferation and survival in hypoxia, and also contributes to the initiation of tumor metastasis as matrix detachment. This effect is also highly linked to lowering the ROS levels to remain away from the cell death threshold. However, to survive under hypoxic conditions, a small portion of cancer cells and/or stromal cells should potentiate their mitochondrial OXPHOS rather than glycolysis to prevent a hostile acidic environment of lactate accumulation, which is the end product of the gly-

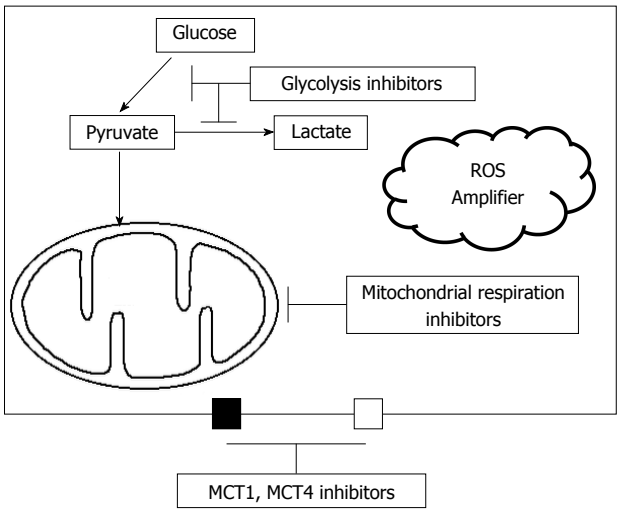

Figure 4 Potential therapeutic targets in metabolic interactions are suggested. A combination therapy might be promising; two targets that block the glycolysis and mitochondrial oxidative phosphorylation or block the glycolysis pathway and amplify ROS levels. Combination treatments targeting both the glycolysis and mitochondrial oxidation, or antioxidant systems can efficiently suppress energy production, or induce ROS-mediated apoptosis. ROS: Reactive oxygen species; MCT: Monocarboxylate transporters.

colytic pathway in hypoxic cancer cells. Thus, even in a hypoxic condition, oxidative cancer cells and/or stromal cells should theoretically exist to support the metabolic fuel for glycolytic cancer cells and handle their waste of lactate *via* the dynamic shuttle of lactate. Tumor heterogeneity exists in tumor mass under hypoxia, and metabolic flexibility is one adaptation mechanism to oxygen gradients (Figure 3).

Treatments against tumor metabolism may aim to target two distinct metabolic pathways of glycolysis and mitochondrial OXPHOS as a combination treatment (Figure 4). Although targeting one specific element of the tumor metabolism could often be ineffective because of the dynamic changes between glycolysis and mitochondrial OXPHOS, targeted treatments against glycolytic-oxidative cell interactions through the inhibition of glycolysis and mitochondrial metabolism might become a promising treatment for advanced stage HCC in clinical practice.

Given the unsatisfactory results of tyrosine kinase inhibitors in HCC treatment, a better understanding of the dynamic interactions between intracellular interactions, such as glycolysis and sensitivity of ROS amplification, and the intercellular interplay, such as glycolytic and mitochondrial OXPHOS cells in cancers, is critical to elucidate the heterogeneous biological features of HCC and identify effective strategies.

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P- Reviewer: Bai G, Echtay KS, Migliaccio E **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wang CH

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