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Review Article

Glucose metabolism and oncogenes in cancer

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Abstract

Cancer cells utilize glucose quite differently from regular cells as cancer cells metabolize glucose more in aerobic glycolysis rather than in oxidative phosphorylation. Whereas aerobic glycolysis is less effective in the metabolism than oxidative phosphorylation. This review aims to explain the mechanisms of cancer metabolism and recent findings related to the subject. There are excessive glycolysis and glucose transport in tumor cells, this situation as known Warburg effect. Mitochondrial impairment, hypoxia, oncogenic signals, and defected metabolic enzymes are mechanisms of this cancer metabolism. Results of increased glycolysis are quick production of ATP and intermediates for biosynthetic pathways and occur acidic cell environment. The oncogenes, hypoxia-inducible factor (HIF), serine/threonine kinase Akt, K-ras, c-myc, AMP-activated protein kinase (AMPK) and p53 have important roles in cancer metabolism. HIF, Akt, K-ras, c-myc, AMPK, and p53 are important oncogenes in cancer metabolism. The differences in metabolism of cancer cells are important targets for new treatment methods.

Keywords: Cancer;glucose; glycolysis; metabolism; oncogenes; warburg effect

INTRODUCTION

Glucose and amino acid glutamine are two of the most abundant metabolites in plasma and together they account for the majority of the carbon and nitrogen metabolism in human cells. Glycolysis is the main mechanism for glucose degradation exists in all cells' cytosol. Glycolysis oxidizes glucose into two molecules of pyruvate, resulting in two moles of ATP and NADH per mol of glucose utilized. The following equation shows the overall glycolytic pathway:

Glucose +2 Pi +2 ADP + 2 NAD^+ →2 Pyruvate + 2 ATP + 2 NADH + $2H^+$ + $2H^2O$

It is unique in that it can act either aerobically or anaerobically, based on the supply of oxygen and the stability of the electron transport chain. Normoxic cells oxidize pyruvate to carbon dioxide in the mitochondria. Pyruvate is converted to lactate by cytoplasmic lactate dehydrogenase (LDH) in hypoxic conditions. In fast-growing cancer cells, glycolysis occurs at a rapid pace, producing significant volumes pyruvate, which is altered to lactate and transferred. It creates a highly acidic environment in the cancer tissue and which is one of the target therapies in cancer (1).

Cancer Metabolism

For the first time, Pasteur suggested that oxygen inhibits glycolysis. But even there is enough oxygen, tumors cells use excessive glucose. Warburg suggested that this situation associated with cancer. Cancer cells transport a high amount of glucose and excessive glycolysis that result in enhance lactate amount even in the existence of enough oxygen. That metabolic situation is named as the Warburg effect. Warburg postulated that it could be due to a defect in the respiratory chain so the tumor cells compensated for this by producing more ATP via glycolysis (1,2).

Although oxidative phosphorylation of glucose provides much more ATP than aerobic glycolysis, it is not fully known why glycolysis is increased in some cancer types. Lactate generation from glucose being 10-100 times higher than complete oxidation of glucose in the mitochondria may be one reason for that (3). Another explanation is glycolysis helps to speed up tumor growth by presenting the components needed to metabolism key elements such as amino acids, carbohydrates, lipids, nucleotides, glycolipids, and glycoproteins. (4).

Positron emission tomography (PET) is used to detect tumors and metastatic lesions (5). PET is based that tumors cells have elevated glycolysis and enhanced glucose transport. Glucose analog 18- fluorodeoxyglucose (18F-FDG) is applied in PET because of tumors cells transport high amount of glucose. Tumors transport less glucose have a better prognosis than transporting more glucose (6).

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Why tumor cells choose aerobic glycolysis rather than oxidative phosphorylation, some other authors asserted that ineffective ATP production and proliferating cells need other important requirements such as amino acids, nucleic acids, lipids for protein synthesis, DNA duplication, and biomembrane synthesis (7). Glycolysis creates acidic surroundings that are deleterious to normal cells but not to cancer cells (8). The other way most of the reactive oxygen species (ROS) are generated in oxidative phosphorylation, glycolysis produces less ROS so the genetic material of cancer cells is protected harmful effects of the excessive amount of ROS, which would cause apoptosis resistance in cancer cells. This is one of the protective mechanisms in malignant diseases and the survival benefit of cancer cells (9).

Beside defective glucose metabolism, also lipid metabolism is defective in tumor cells. Normal cells provide fatty acids mainly from dietary sources. But cancer cells have an important increase in de novo fatty acid production. ATP citrate lyase activity and fatty acid synthase (FASN) are enhanced to facilitate the production of fatty acids. An enzyme catalyzing monoacylglycerol to reveal glycerol and a free fatty acid is excessive present in cancer cells that increase the aggressiveness of tumors and increase the amount of free fatty acids (10,11).

In cancer cells, one of the reasons for higher glycolytic rate is upregulation of the glucose transporter 1 (GLUT1) so an increase in glucose uptake (12,13). Also, the upregulation of GLUT1 is linked with poor survival and tumor aggressiveness (14-16). Besides, GLUT1 expression is linked with 18F-FDG uptake so, which is higher in positive lesions than negative ones in positron emission tomography (PET) (17). GLUT1 is also a significant part of anticancer therapy (18).

According to some studies, tumor cells have fewer mitochondria than normal cells and that they contain a mitochondrial-bound isozyme of hexokinase (HK-2) that is not subject to feedback control, allowing increased uptake of glucose. Hexokinase plays an important role in homeostatic processes like apoptosis. Tumor cells exhibit a different isozyme of pyruvate kinase (PK). Normal cells contain PK-1 and tumor cells contain PK-2; they are generated through alternative splicing of the same gene expression. Enhanced production of M2 isoform of pyruvate kinase and fosforilation of that is associated with or leads to less production of ATP (Figure 1) (19). It also is thought to allow increased use of metabolites supplied by glycolysis for building up the biomass (proteins, lipids, and nucleic acids, etc) required for the proliferation of cancer cells (1,20).

Defects in genes of the tricarboxylic acid cycle enzymes showed in the different tumors, such as succinate dehydrogenase (SDH) which catalyzes the transfer succinate to fumarate to release one molecule flavin adenine dinucleotide, and fumarate hydratase (FH) which convert fumarate to malate, enzymes defects. These defects increase metabolites like succinate and fumarate. These metabolites inhibit HIF-1 suppressing enzyme proline hydroxylase and activate the HIF pathway. Activation of HIF related to the first step of tumor metastasis (21). SDH defects linked with head and neck paragangliomas and FH defects associated with several forms of malignant cancers occurred in various tissues, such as uterine leiomyomatosis, cerebral cavernomas, and breast cancer (22,23). Some mitochondrial respiratory enzymes are found significantly lower in the different groups of human cancers correlate with an increase of aggressiveness, invasiveness, and metastasis of tumor cells (24).

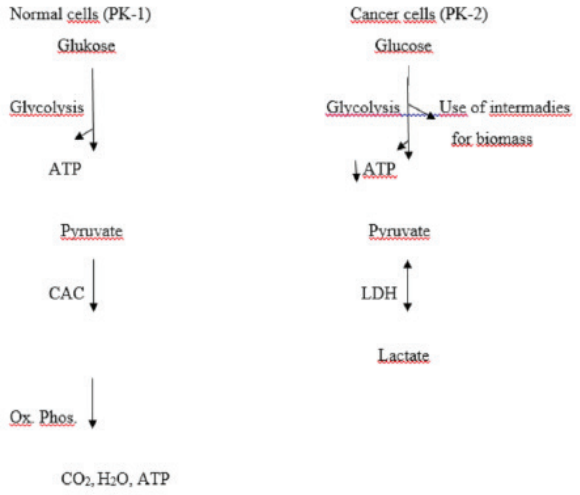

Figure 1. Pyruvate kinase isozymes and glycolysis in normal and cancer cells. (CAC: citric acid cycle, OX PHOS: oxidative phosphorylation) (1)

HIF

HIF-1 is a transcription factor that controls the genes involved in hypoxia-induced metabolic switching, tumor pH modulation and angiogenesis (25) HIF stimulates a large group of genes such as glucose uptake protein and glucose metabolism enzymes, extracellular pH regulation, angiogenesis, erythropoiesis, and mitogenesis that promote cell survival. HIF comprises two subunits, α subunit breaks down quickly under normoxic situations, however, the other subunit (β) is stable (26).

Despite angiogenesis, many solid tumors have localized areas of poor blood supply and thus show high rates of anaerobic glycolysis. Hypoxia in areas of tumors with poor blood supply stimulates a transcription factor complex, named hypoxia-inducible factor-1 (HIF-1), which modulates the adaptation of cells to hypoxic conditions. This transcription factor whose activity is turned on by low oxygen tension up-regulates activities of at least eight genes controlling the synthesis of GLUT1 and glycolytic enzymes such as aldolase, phosphoglycerate kinase, phosphofructokinase, pyruvate kinase and lactate dehydrogenase-A (LDHA). Hypoxia and hypoxia-inducible factor (HIF) causes enhanced glycolysis and tumorigenesis. HIF additionally decreases mitochondrial respiration and contributes downregulation of the TCA cycle (1,14,27).

Hexokinase catalyzes the first stage in the glycolytic process where glucose is converted to glucose-6-phosphate by transferring one phosphate group from ATP. Hexokinase II, the target of HIF-1 is over-expresses in the hypoxic solid tumor (28). HIF alters glucose metabolism even under normoxic conditions. Also, HIF-1 overexpression is associated with worse survival in some solid tumors (29). HIF-1 overexpression increases resistance to radiotherapy and patient mortality in oropharyngeal and esophageal squamous cell carcinoma, laryngeal, gastric, pancreatic, colorectal, and rectal carcinoma (30,31). Oncogenes and tumor suppressor genes mutations stimulate HIF-1 and some other glucose metabolism elements regardless of hypoxia. Some of them are explained below.

Akt and K-ras

Serine/threonine kinase Akt triggers aerobic glycolysis by influencing several molecules specifically participated in glycolysis without affecting mitochondrial respiration. This supports both adaptations to limited oxygen flux and cancerous cells stimulate the development of the metabolic intermediates needed for rapid proliferation. Akt enhances the aerobic glycolysis of both hematopoietic and glial neoplastic cells. Tumor cells carrying triggered Akt uniquely experience accelerated cell death under low glucose environments. (32). Akt stimulates over-expressions and membrane localization of GLUT1 which transports glucose into the cell and the most widely expressed glucose transporter (33).

Pyruvate is the final product of glycolysis and can be transformed into acetyl-CoA by pyruvate dehydrogenase complex and that is transferred to citrate in mitochondria. ATP citrate lyase cleave citrate to acetyl-coenzyme A in the cytoplasm that beginnings of fatty acid synthesis. Stimulated Akt increases de novo synthesis of fatty acids from pyruvate by affecting ATP citrate lyase however Akt inhibition reduces the production of the fatty acids (34).

GLUT1 expression enhanced in cells with mutated K-Ras. So, glucose uptake and utilization, and lactate production increase but oxidative phosphorylation and mitochondrial functions don't affect. K-Ras mutated cells show long survive when grown in low glucose conditions. This finding was thought that agents inhibiting glucose metabolism can kill only K-Ras mutated cells. For example, hexokinase inhibitor 3-bromopyruvate is much more toxic to some cancer cells carrying K-Ras mutation, however, it is less harmful to cells without K-Ras mutations (35).

C- myc

C-myc is a crucial growth control gene that is impaired by chromosomal translocation and gene amplification in cancer cells. C- myc overexpression is present in multiple human cancers such as colon, breast, prostate, and bladder tumors (36-38). It is estimated that c-myc overexpression leads to the origin of at least forty percent of all human cancers. C-myc stimulates most of the genes of glycolytic enzymes, such as hexokinase II, phosphofructokinase, enolase 1, LDHA, and GLUT1 (39-42). LDH converts pyruvate to lactate under limited oxygen and helps tumor cells to survive under hypoxic conditions. So c-myc enhances glucose uptake and lactate production. Also, c-myc increase oxidative metabolism of glucose and activates pyruvate dehydrogenase so occur excessive acetyl-CoA (41).

AMPK

AMP-activated protein kinase (AMPK) is a metabolic essential enzyme present in all eukaryotic cells. AMPK is a reduced power checkpoint. AMPK is stimulated in situations of low ATP and enhanced AMPs such as hypoxia. AMPK inhibits protein, cholesterol, and fatty acid production. AMPK phosphorylation inactivates HMG co-reductase and acetyl CoA carboxylase enzymes which essential synthesis of cholesterol and fatty-acid (43). AMP-Activated protein kinase (AMPK) stimulates catabolic situations like beta-oxidation of fatty acids and inhibits anabolic situations like nucleotide and fatty acid synthesis (44).

p53

p53 is the most essential tumor suppressor gene and plays a major role in normal growth and proliferation, including activation of apoptosis, cell cycle control, DNA repair, and preservation of genome consistency. p53 gene deficiency or loss is linked with the bulk of cancers. p53 has a significant function in the management of glycolysis and oxidative phosphorylation. p53 affects metabolic components such as glycolytic and TCA cycle enzymes and various glucose transporters. p53 prevents excessive glycolysis and decreases the rise in glycolysis that is typical of tumors. (45).

p53 can suppress glucose transport by repressing GLUT1, GLUT3, and GLUT4 (46,47). p53 also suppresses the insulin receptor promoter, thus potentially inhibiting glucose intake by reducing the insulin receptor (48). p53 also prevents the transfer of lactate, contributing to the aggregation of lactate, which reduces the glycolytic intensity (49). Loss of p53 enhances glycolysis due to the loss of cytochrome oxidase 2 $(SCO)^2$ that is important for mitochondrial respiration. Activation of TP53-induced glycolysis and apoptosis regulator (TIGAR), a p53-regulated gene, decreases the level of fructose-2,6-bisphosphate which represses glycolysis. P53 stimulates oxidative phosphorylation through TIGAR. TIGAR is a new isoform of PFK-2 (50,51). Loss of p53 causes increased phosphoglycerate mutase (PGM) expression, which activates glycolysis (52). p53 also activates AMPK which plays a crucial function in the homeostasis of cellular energy (53,54). Additionally, p53 stimulates miR-34a, a blocker of many glycolytic enzymes and autophagia, by triggering multiple autophagia-related genes (55,56).

Treatment

As explained above the metabolic features of tumor cells significantly distinct from normal cells. Cancerous cells are more reliant on aerobic glycolysis, fatty acid synthesis, and glutamine. Studies demonstrate that tumor cells differ from normal cells prone to metabolic alterations are sensitive to inhibition of glycolysis giving a therapeutic chance and this cell metabolism is related to drug resistance.

Increased glycolysis causes much more pyruvate and than lactate so leads to acidification around the tumor. This acidified environment causes resistance to chemical drugs (57). pH and oxygen tension in tumors are important factors affecting the actions of anti-cancer drugs and other treatments. Chemicals have been developed to inhibit glycolysis in tumor cells. Although found to have variable effectiveness in preclinical studies, so far none of them have attained much clinical use. They include 3- bromopyruvate (3BP), a blocker of HK-2, and 2-deoxy-D-glucose, a blocker of HK-1. Besides HK2, 3BP also selectively blocks the Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), another essential enzyme in glycolysis, lead to major cellular ATP loss and death of cells (58). Anti-cancer drugs such as methylprednisolone, cisplatin may synergize with 2-deoxy-D-glucose to suppress cell proliferation and cause apoptosis (59,60). Dichloroacetate (DCA) inhibits the activity of pyruvate dehydrogenase kinase and so stimulates the activity of pyruvate dehydrogenase diverting substrate from glycolysis into the citric acid cycle (1).

CONCLUSIONS

As above explained differences in cancer metabolism offer us a therapeutic chance. Treatments targeting oncogenes HIF, Akt, K-ras, c-myc, AMPK and p-53 can be provided powerful alternative therapies. So development in this area should be followed and new letters should be published. Maybe the treatment of cancer will be taken important steps in this curious area.

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