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High Rate of Glycolysis and Cancer

Kathryn Jinmei Tian*

Faculty of Medicine, Boucher Institute of Naturopathic Medicine, New Westminster, Canada

Abstract

One hundred years ago, abnormal metabolism of cancer cell was regarded as one of the most important pathological features of malignancy. Recently, with the development of system biology, researchers regained the interest in regulating cancer metabolism. In 1920s', Dr. Otto Warburg discovered that, even when oxygen is ample, malignant cells still prefer the anaerobic glycolysis, and the rate of glucose uptake is high while the overall glycolysis increases. Cancer cells divide faster than normal cells, hence they need more bioenergy, and they need to change their metabolism to produce the extra energy. In recent 20 years, the link between high rate of glycolysis and cancer was re-evaluated and has inspired enthusiasm upon research into the metabolism of cancer cells. Novel diagnostic methods and new drugs were created by the understanding of the features of cancer metabolism. Glycolysis in cancer cells has clinical implications in cancer diagnosis, treatment and prognosis. The purpose of this review is to focus on the mechanism of high rate of glycolysis in cancer and its significance in cancer diagnosis and therapies. The regulatory network of cancer is complex, system biology might help us to find the clue. There are evidences showing that mixture of drugs has therapeutic advantages in clinical practice. Combinations of anti-neoplasm drugs have already been administered with encouraging results. Therefore, the multi-targeted MCA advised therapy might be the most promising strategy for cancer. The study for novel inhibitors from medicinal herbs are now ongoing. We believe, there will be more and more therapeutic strategies coming in the near future to help human beings fighting with cancer.

Keywords: Cancer; Glycolysis; Malignancy; Cancer metabolism; Cancer cells; Tumor

Introduction

Cancer cell metabolism is an old pathogenetic issue that has recently gained new interest as target for therapeutic approaches. In 1920s', Dr. Otto Warburg discovered that malignant cells generally have altered metabolism with high rates of glucose uptake and increased glycolysis, even under aerobic condition. Cancer cells display a variety of changes in their metabolism, which enable them to satisfy the high bioenergetic and biosynthetic demands for rapid cell division. In recent 20 years, the link between high rate of glycolysis and cancer was re-evaluated and has inspired enthusiasm upon research into the metabolism of cancer cells. Novel diagnostic methods and new drugs were created by the understanding of the features of cancer metabolism.

What is the relationship between cancer cell metabolic changes and the cancer progression? Can we target the metabolic changes to control cancer? Can we use its feature to diagnose cancer and predict the prognosis? Glycolysis in cancer cells has clinical implications in cancer diagnosis, treatment and prognosis. The purpose of this review is to focus on the mechanism of high rate of glycolysis in cancer and its significance in cancer diagnosis and therapies.

Literature Review

Mechanisms leading to high rate of glycolysis in cancer

More than 80 years ago, Dr. Otto Warburg observed and described the hallmark of tumor metabolism which is featured by anaerobic glycolysis, or Warburg effect. In normal cells, the glucose is catabolized mainly by aerobic pathway, one glucose can produce about 38 ATP. Only when in an oxygen-deprived environment, the anaerobic pathway will be used, and the pyruvate is converted to lactate, only about 2 ATP can be produced. In cancer cells, even when oxygen is ample, the anaerobic pathway is still preferred. So, less bioenergy will be produced, and the production is very inefficient. Hence, the cancer cells need to intake more glucose and accelerate the metabolic rate [1]. The *in vivo* study showed that cancers take up tenfold more glucose than normal tissues. The researchers confirmed this metabolic phenotype by PET observation using F-18-2-fluoro-deoxy-glucose [2].

Is the Warburg effect a consequence or a cause of tumorigenesis? Experimental and clinical studies have demonstrated the correlation between the abnormal metabolism and malignancy initiation and progression, but the underlying mechanisms leading to the Warburg phenomenon were still largely unknown. Some research showed the link to mitochondrial abnormalities, upregulation of rate-limiting enzymes/proteins in glycolysis, intracellular pH balance, hypoxia-induced switch to anaerobic metabolism, and metabolic reprogramming after loss of p53 function [3]. The discovery of mitochondrial tumor suppressor genes may conform to Warburg's hypothesis [4]. Some evidences showed that the interplay between microRNAs and oncogenes/tumor suppressors, via key metabolic enzyme effecters, could facilitate the Warburg Effect in cancer cells [5]. According to the Darwinian evolutionary theory, the environment imparts pressure to select for species that are most fit within that specific microenvironmental context. The anaerobic glycolysis results in a high rate of lactic acid production; resulting in acidification of the extracellular space. Evidence has shown that low extracellular pH is a strong negative prognostic indicator of metastasis-free survival. So, it might be the cancer cells' choice to have a high rate of glycolysis [6].

Nevertheless, the concept of anaerobic glycolysis as the paradigm of tumor cell metabolism has been challenged, as some tumor cells

***Corresponding author:** Kathryn Jinmei Tian, Faculty of Medicine, Boucher Institute of Naturopathic Medicine, 435 Columbia St, New Westminster, BC V3L 5N8, Canada, Tel: +1 604-777-9981; E-mail: ktian@binm.org

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exhibit high rates of oxidative phosphorylation. Since Warburg proposed that it is the mitochondrial damage causing cancer cells exhibiting increased glycolysis, many researchers believed that the main energy source for cancer cell processes is the ATP production by glycolysis. However, when using glycolytic inhibitors in chemotherapy, cancer cell proliferation was not significantly suppressed. This might indicate that the Warburg hypothesis is not applicable to all kinds of malignancy and the principal ATP production may derive from active oxidative phosphorylation no matter if the rate of glycolysis is high or not. Some studies even demonstrated that most cancer cells do contain metabolically efficient mitochondria. Cancer cells do need the functional mitochondria to provide ATP and intermediate to keep the high proliferation rates [7]. Recent research showed that overexpression of the human DEK oncogene reprograms keratinocyte metabolism to fulfill energy and macromolecule demands required for cancer cell growth; DEK expression is necessary for the transcription of several metabolic enzymes involved in anabolic pathways, hence increases the cellular acidification rates, a readout of glycolysis; at the same time, DEK overexpression increases the maximum rate of oxygen consumption and therefore increased the potential for oxidative phosphorylation [8].

So, according to the research we analyzed here, the metabolic changes in cancer cells are extensive and complex; more research needs to be done to clarify the biochemical basis for the Warburg effect.

High rate of glycolysis and cancer diagnosis/prognosis

The rate of glycolysis and the demand for glucose in cancer cells are higher than that in normal cells. This characteristic can be utilized for *in vivo* imaging to facilitate cancer diagnosis; and, it can enable us to estimate the prognosis of cancer; also, many cancer markers were in use based on the Warburg effect. Research showed that overexpression of TIMM9 (a mitochondrial inner membrane protein translocase of inner mitochondrial membrane 9 homolog) and the cancer vascular invasion has a borderline association (p=0.0887). Overexpression of TIMM9 is used as an independent prognostic marker for gastric carcinoma (p = 0.011) via the multivariate Cox regression analysis [9]. A recent research investigated the synthesis of near-infrared (NIR) fluorochrome IR-822-labeled 2-amino-2deoxy-o-glucose (DG) for optical imaging of tumors in mice. Results demonstrated that IR822-DG actively and efficiently accumulated at the site of the tumor. The study indicated the broad applicability of IR-822-DG for cancer diagnosis [10]. In clinical research on human breast, brain, and prostate cancers and in experimental animal models, magnetic resonance spectroscopy (MRS) has been used to study cancer metabolism. MRS can determine specific genetic and metabolic changes that occur in malignancy. Therefore, the metabolic markers which are identified by MRS can provide information on biochemical changes in cancer cells to decide different metabolic cancer phenotypes. The contrast-enhanced Magnetic Resonance Imaging (MRI) has a high sensitivity for cancer diagnosis. When using MRS and MRI together, the *in vivo* magnetic resonance spectroscopic imaging (MRSI) can improve the diagnostic specificity of human cancers. MRS has become an important imaging test for cancer diagnosis and management [11].

Based on the biochemical feature of high rate of glycolysis in cancer, there will be more and more cancer diagnostic methods invented in the future.

High rate of glycolysis and cancer treatment

The treatment effect of cancer chemotherapy is not satisfactory. Cytotoxic strategy might not be enough to control cancer. Treatments aiming at metabolism regulation, especially at regulating glycolysis to deprive the energy supply to cancer cells have regained the interest of scientists. Many glycolytic enzymes and transporters can be candidate targets for cancer therapy based on the growing evidence. Actually, during the last decade, the research and development of anticancer medications are largely under the consideration of cancer cell metabolic regulation.

There are new drugs being invented to regulate the glycolysis or other metabolic pathways. Some old drugs were re-evaluated and resumed the usage. Other research also indicated that anti-diabetes medication might be of help in cancer treatment. To stimulate glycolysis, a family of regulatory bifunctional 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatases (PFKFB) needs to be activated by over-expression of HIF-1 alpha and myc, activation of ras and loss of p53 function. The PFKFB enzymes can synthesize fructose-2,6-bisphosphate (F2,6BP). F2,6BP can allosterically activate 6-phosphofructo-1-kinase (PFK-1) which is the rate-limiting enzyme for glycolysis. When energy is abundant (i.e. ATP is of big quantity.), PFK-1 is inhibited according to the reciprocal regulation. F2,6BP can override this inhibition so that F2,6BP can enhance glucose uptake and glycolytic pathway. Hence, the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatases are targeted for the development of anticancer drugs [12]. Hexokinase (HK) is the rate-limiting enzyme for converting glucose to glucose-6-phosphate while Hexokinase 2 (HK2) is the Hexokinase which expresses at higher level and is most closely related to malignant tumor. Research showed that Benserazide (Benz) was identified as a selective HK2 inhibitor which can specifically bind to HK2 and significantly inhibit HK2 enzymatic activity *in vitro*. At the same time, *in vivo* study demonstrated that intraperitoneal injection of Benz at 300 and 600 mg/Kg suppressed cancer growth in tumor-bearing mice and there was no toxicity identified [13]. Lonidamine is an inhibitor of glycolysis and 6-diazo-5-oxo-L-norleucine (DON) is an inhibitor of glutaminolysis. They are two old drugs that were abandoned about fifty years ago when the importance of cancer metabolism was not fully understood, and clinical trial methodology was underdeveloped. According to a review study, lonidamine and DON are safe to use and they might be effective in treating cancer [14]. Metformin is a drug for treating diabetes. It has been widely used for diabetics for more than forty years. Metformin can mimic caloric restriction acting on cell metabolism at multiple levels. It can reduce all energy-consuming processes in the cells including cell proliferation. Scientists are researching into the possibility to use metformin for cancer prevention and treatment [15].

Although cancer metabolism regulation is a promising strategy for cancer control, this approach has a drawback: that is, antiglycolytic agents may cause serious side effects because they can inhibit the glycolysis in normal cells as well. The selective action against cancer cells is still a difficult issue waiting to be solved. Another concern is that the treatment effect with glycolytic inhibitor monotherapy is poor. Scientists are now considering using combination therapy to achieve better anticancer effect. A new method called metabolic control analysis (MCA) of cancer cells can be used to analyse how multiple steps sharing the control of energy metabolism. By applying MCA, scientists are now able to identify the group of proteins (and genes) that should be modified at the same time, so that the whole metabolic system(pathway) can be regulated. For quite a while, the specificity is the most important requirement in the design of drugs (i.e. the drug needs to specifically inhibit a single controlling step); the new task is to design unspecific drugs or drug mixtures which will target multiple sites in the metabolic pathways in cancer cells [16].

Discussion

Based on this systematic point of view, researchers are also trying to find novel strategies from food, vitamins and plants. Ketogenic diet (KD) is composed of high fat (big amount of monounsaturated and polyunsaturated fats), adequate protein (low to moderate amount), and low carbohydrate (non-starchy vegetable carbohydrate). KD is low in carbohydrate, it might induce cancer cell starvation and apoptosis based on the Warburg effect; at the same time, KD provides adequate protein and high fat which can be broken down to be the energy source in normal cells but not in cancer cells [17]. Research showed that the combination of vitamin C and a quinone undergoing a redox cycling (vitamin K-3) leads to an oxidative stress that kills cancer cells in a selective manner [18]. Plants are a good source for inventing new drugs. Phytometabolites (functional elements derived from plants) can exert the functions like anti-cancer, anti-inflammatory and anti-oxidant. The feature of phytometabolites' anti-cancer effect is that they can target multiple signaling pathways. Recent observations showed that some phytometabolites could target metabolic-related enzymes in cancer cells so that they can control cancer growth by regulating the abnormal metabolism in cancer cells, with little or no harm to normal cells [19]. Anemone rivularis Buch (ARE) have been used as a traditional remedy for treatment of inflammation and cancer. A recent research showed that ARE can inhibit a variety of cancer cells, including MDA-MB321, K562, HT29, Hep3B, DLD-1, and LLC. In *in-vitro* kinase assay, ARE suppressed PDHK activity and inhibited aerobic glycolysis by reducing phosphorylation of PDHA in human DLD-1 colon cancer and murine LLC cells [20].

Conclusion

Cancer is complex, and its metabolic change is multifaceted. The system biology approach is promising because it can help us targeting multiple steps in the pathway instead of aiming at just one step. Clinical practice has anticipated the strategy of using a group of drugs together. Combinations of anti-neoplasm drugs have already been administered with encouraging results. Therefore, the most promising strategy for cancer treatment seems to be that of a multi-targeted MCA advised therapy. (16) The study for novel inhibitors from medicinal herbs are now ongoing. Dr. Ha said, "In addition, I have found several novel inhibitors against LDHA and PDHK activity from library of ingredient compounds isolated from medicinal herbs." And, Dr. Ha's research team has another paper in this issue: Myristica fragrans Suppresses Tumor Growth and Metabolism by Inhibiting Lactate Dehydrogenase A. Am J Chin Med. 2016;44(5):1063-79 (personal information, Dr. Ha, Director of Department of Korean Medical Science, School of Korean Medicine and Director of Healthy Aging Korean Medical Research Center)

We believe, there will be more and more therapeutic strategies coming in the near future to help human beings fighting with cancer.

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