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Critical Reviews in Oncology/Hematology 92 (2014) 312–321

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Phosphofructokinase: A mediator of glycolytic flux in cancer progression

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Accepted 13 May 2014

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Abstract

In view of the current limitations of cancer chemotherapy, there has been resurgent interest in re-visiting glycolysis to determine whether tumors could be killed by energy deprivation rather than solely by strategies to inhibit proliferation. Cancer cells exhibit a uniquely high rate of glucose utilization, converting it into lactate whose export subsequently creates an acidic extracellular environment that is thought to promote invasion and metastasis, in preference to its complete oxidation even in the presence of adequate oxygen supply. Reductive analysis of each step of glycolysis shows that, of the three rate limiting enzymes of the pathway, isoforms of phosphofructokinase may afford the greatest opportunity as targets to deprive cancer cells from essential energy and substrates for macromolecular synthesis for proliferation while allowing normal cells to survive. Strategies discussed include restricting the substrate for this enzyme. While prospects for monotherapy with glycolytic inhibitors are poor, combination therapy may be productive.

Keywords: Cancer; Aerobic glycolysis; Fructose-1,6-bisphosphate; PFK

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http://dx.doi.org/10.1016/j.critrevonc.2014.05.007
1040-8428/

1. Introduction

In cancer chemotherapy, traditional cytotoxic drugs generally target the rapid proliferative activity of tumor cells to distinguish them from normal cells. However, this does not avoid significant toxicity to normal tissues that have a high turnover rate such as the immune cells, the GI tract and hair, greatly limiting the efficacy of such agents. The advent of genomics is shifting the focus toward identification of more subtle differences that could be exploited. In terms of possible therapeutic utility, one aspect that is receiving renewed attention is the functional distinction in metabolic activity between normal and cancerous cells. Otto Warburg, in his groundbreaking studies in the early1920s [1] (for which he was later to be awarded the Nobel Prize in 1956), first noted that tumors had a particularly high requirement for glucose, in their hypoxic environment, converting it into lactate. Unlike normal cells however, which derive ATP from anaerobic glycolysis as a short term measure, for example during vigorous muscle activity, return to normoxic conditions does not cause a significant switch of the lactate back to pyruvate in tumors. This has become known as the 'Warburg effect' or 'aerobic glycolysis' whereby cancer cells apparently prefer to derive their ATP (albeit inefficiently) from glycolysis, reducing their reliance on oxidative phosphorylation even in the presence of sufficient oxygen supply. For example, leukemic cells, although residing within the blood stream at high oxygen tension, exhibit the Warburg effect [2]. This unique dependence on glucose is the basis for the clinical imaging of metastatic cancers through application of positron emission tomography of 2-[^{18}F]fluoro-2-deoxy-glucose (FDG-PET) [3,4]. Increased glucose uptake correlates with tumor aggressiveness and poor prognosis [5].

1.1. Expression of hypoxia inducible factor (HIF) in cancer

As malignant cells proliferate and expand, cells within the core of the tumor are deprived of blood vessels. Consequently, diffusion of substrates including oxygen and glucose becomes limited within the center of the cellular mass, leading to development of hypoxia. This results in the stabilization of the hypoxia-inducible-factors (HIFs) primarily HIF-1 and HIF-2, which consist of two subunits α and β. HIF1α and 2α both dimerize with HIF1β and bind to hypoxia-responsive elements in promoters of target genes, initiating a transcriptional program to overcome the hypoxic stress [6,7]. Under the effect of HIFs, the tumor produces angiogenic factors such as VEGF to promote increased vascularity within the stroma. Carcinoma *in situ* is unable to promote angiogenesis due to the presence of the basement membrane [8]. Only when this is breached, does the tumor promote new vessels growth directly within the stroma and become vascularized and exposed to a normoxic environment. Therefore in the early stages of cancer, angiogenesis fails to relieve hypoxia.

There is an interesting symbiosis between the well-oxygenated outer regions undergoing oxidative phosphorylation with the poorly oxygenated core that maintains lactate production. The lactate produced from hypoxic cells is taken up as energy substrate by the well-oxygenated cells *via* monocarboxylate transporter 1 (MCT1), freeing these cells from glucose dependence, allowing more glucose availability to the hypoxic cells [9]. Such mechanisms could also explain apparent switches from the Warburg effect to oxidative phosphorylation under limiting glucose conditions in glioma cells [10].

The molecular mechanisms leading to constitutive up-regulation of glycolysis are not well understood. Warburg [11] had hypothesized that the deviation in cancer cell metabolism was due to mitochondrial defects but this simple explanation has been discounted. Several studies have reported that oncogenic activation and tumor suppressor mutations can give rise to the Warburg effect either directly or indirectly, through activation of HIF-1 independently of hypoxia [7]. Direct activators include *ras*, *myc*, Akt and p53 [12]. Ras promotes glycolysis, while myc up-regulates expression of various metabolic genes [13,14] and interacts directly with hexokinase 2 [16]. Akt kinase also has a role in glucose uptake and utilization in cancers [15,16] showing that the activation of Akt alone is sufficient to drive high glucose uptake and the Warburg effect. p53 can inhibit anaerobic glycolysis and stimulate oxidative phosphorylation through transcriptional activation of TIGAR, a glycolytic inhibitory protein [7]. Loss of p53 correlates with increased glycolytic activity [17,18]. Other oncogenic pathways may cause non-hypoxic expression of HIFs through activation of mTOR [7,12].

HIF-1 up-regulates the expression of over 80 genes that are critical in glucose metabolism, cell survival, tumor angiogenesis, invasion and metastasis [19,20]. Nearly all glycolytic genes are transcriptional targets of HIF; transcriptional expression of subunit HIF-1α is under the control of growth factor signaling pathways involving PI3K/Akt/mTOR and Raf/MAPK [21–23]. HIF-1α is usually degraded under normoxic conditions but stabilized in tumors even under non-hypoxic conditions [19,24,25] as a consequence of oncogenic activation of PI3K/Akt, *src* and *ras* or inactivation of tumor suppressor VHL leading to the Warburg effect [23,24]. Reduction of HIF-1α could be a promising anticancer strategy [19,22].

1.2. Upregulation of glycolysis in cancer

The advantages of maintaining a high rate of glycolysis in tumor cells is still incompletely understood in metabolic terms. Certainly the extrusion of accumulated lactate through multiple families of H^+ transporters [26] to prevent acidosis induced apoptosis, creates an acidic microenvironment harmless to themselves, yet fatal to competing populations of