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Deregulation of Energy Metabolism as a Cause and Consequence of Oncogenic Process: Review of Literature

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Abstract

The reprogramming of energy metabolism is an emerging hallmark of cancer that has not yet been demonstrated in all tumor models, and there are aspects which still not entirely clear. This review enrolled and analyzed data from the last 20 years regarding the proposed theme; and it allowed to conclude that the deregulation of energy metabolism is a key factor in the initiation and progression of tumors, behaving as a cause and consequence.

Keywords: Glycolysis; Warburg phenomenon; Energy metabolism; Cancer

Introduction

The chronic and often uncontrolled cell proliferation that represents the essence of neoplastic disease involves not only deregulated control of cell proliferation but also corresponding adjustments of energy metabolism in order to fuel cell growth and division. Under aerobic conditions, normal cells process glucose, first to pyruvate via glycolysis in the cytosol and thereafter to carbon dioxide in the mitochondria; under anaerobic conditions, glycolysis is favoured and relatively little pyruvate is dispatched to the oxygen-consuming mitochondria. Otto Warburg first observed an anomalous characteristic of cancer cell energy metabolism: even in the presence of oxygen, cancer cells can reprogram their glucose metabolism, and thus their energy production, by limiting their energy metabolism largely to glycolysis, leading to a state that has been termed "aerobic glycolysis" [1]. In addition, the cancer cell uses high amounts of glucose as carbon source for anabolic reactions [2]. Although the Warburg phenomenon is not universally demonstrated in all tumor models, however, the increase in glucose uptake is frequent in the oncogenic process, which is evidenced by positron emission tomography (PET) using a as radiotracer fluorodeoxyglucose (FDG) glucose analogue molecule that by not completing your metabolism ends up in the cell, so it can be measured or quantified [1,2].

The reprogramming of energy metabolism confers proliferative advantage to the cancer cell for the following reasons:

If the tumor cell up-regulates via glycolytic acquires the ability to withstand the fluctuating oxygen tensions [3].

Reprogramming energy produces significant amounts of lactate acid generating a microenvironment that promotes tumor invasion [4] and anticancer immune effector suppresses [5].

Cancer cell benefits from normal cell metabolism, because the lactate which is produced by tumor cells may be captured by stromal cells via monocarboxylate transporter (MCT1 and MCT2) to regenerate pyruvate. This pyruvate can be extruded and recycled by the cancer cell or can be used for oxidative phosphorylation (OXPHOS) [6] (Figure 1). This arrangement generates a microecosystem in which aerobic and anaerobic components are in a complementary metabolic pathway that promotes growth and survival of tumor cells.

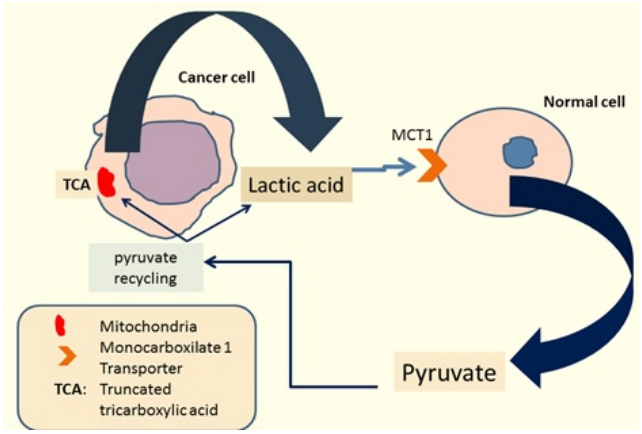

Figure 1: Metabolic cooperation between cancer cell and normal cell.

Tumors can metabolize glucose through the pentose phosphate pathway (PPP) to generate nicotinamide adenine dinucleotide phosphate (NADPH) that ensures the cell's antioxidant defenses against a hostile microenvironment and chemotherapeutic agents [7]. Moreover, NADPH can contribute to fatty acid synthesis [2] which they are important to maintain lipid membranes.

Cancer cells use intermediates of the glycolytic pathway for anabolic reactions (for instance, glucose 6-phosphate for glycogen and ribose 5-phosphate synthesis, dihydroxyacetone phosphate for triacylglyceride and phospholipid synthesis, and pyruvate for alanine and malate synthesis) [8]. Moreover in proliferating cancer cells, pyruvate may enter a truncated tricarboxylic acid (TCA) cycle (Figure 1). The net result of this truncated TCA cycle is that acetyl-CoA is exported from the mitochondrial matrix and becomes available for the synthesis of fatty acids, cholesterol, and isoprenoids [2].

Thus, the entire metabolism (in particular glycolysis and the TCA cycle) is reorganized to augment anabolic reactions linked to cell growth and proliferation.

The molecular mechanisms that underlie metabolic reprogramming of cancer cells are complex. Among the factors set are: 1) activation of hypoxia inducible factor (HIF), a transcription factor that is activated by hypoxic stress but also by oncogenic, inflammatory, metabolic, and oxidative stress (Figure 2); and 2) mitochondrial DNA (mtDNA) mutations which condition OXPHOS defects, favoring the aerobic glycolysis and production of reactive oxygen species (ROS), generating a state of metabolic and oxidative stress (Figure 3). Two factors that promote the expression of HIF, it acts as a promoter of aerobic glycolysis [2].

The over-regulation of aerobic glycolysis is therefore a key factor in oncogenesis, since as will be expanded later; aerobic glycolysis may not only be a consequence of tumor process but also a determinant in the onset and progression of oncogenic process. Therefore, the objective of this review is to quote and develop evidence supporting the reprogramming of energy metabolism in the cancer cell would be cause and consequence of the tumor process.

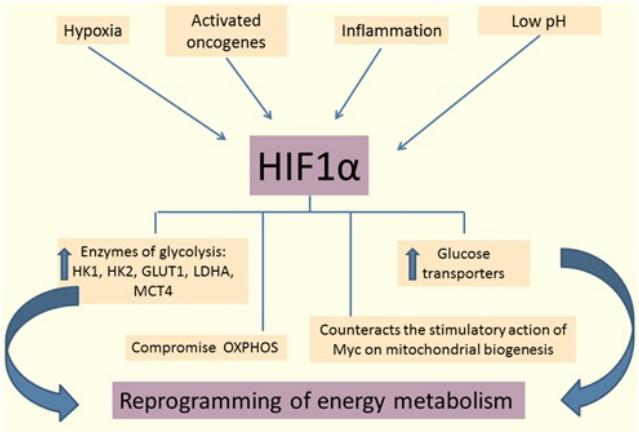

Figure 2: Factors that up-regulated the expression of HIF1α. When HIF1α accumulates, joins and promotes expression of target genes such as enzymes of glycolysis and glucose transporters, glycolytic metabolism promoting. HK1: hexokinase 1, HK2: hexokinase 2, GLUT1: glucose transporter, LDHA: lactate dehydrogenase, MCT4: lactate-extruding enzyme monocarboxylate transporter 4.

Material and Methods

The PubMed database to search for information concerning the subject proposed was used, using the keywords: Glycolysis, Warburg phenomenon, Energy metabolism and cancer. Publications of the past 20 years, under the category of review, experimental and clinical studies were selected.

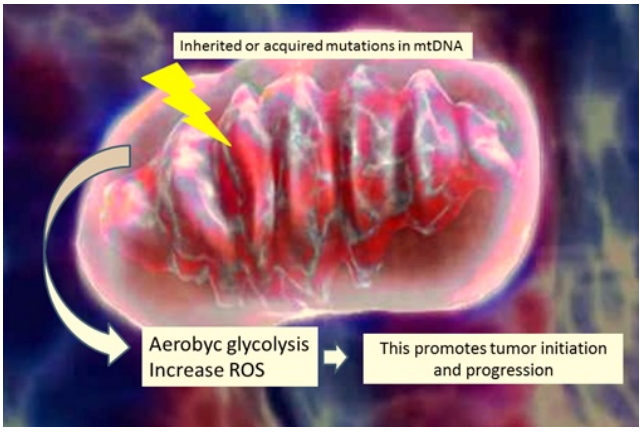

Figure 3: Consequences of an aberrant / OXPHOS truncated by inherited or acquired mutations in mtDNA.

Results

Over-regulation of aerobic glycolysis as a cause of oncogenic process

In a study published in 2007, Zhou et al. [9], showed the presence of mutations in mtDNA from a collection of biopsies from head and neck carcinomas. They found that expression of a mutant ND2 (2 subunit NADH dehydrogenase mutant) correlated with a phenotype glycolytic aerobic, accompanied by an increased production of reactive oxygen species [9]. This means that if a cell holder inherited or acquired defects in specific mtDNA sequences, the OXPHOS result in an aberrant process and truncated [10], resulting in an overproduction of ROS and upregulation of aerobic glycolysis which end producing a metabolic status and oxidative stress. The cell enters metabolic stress due to increased glycolysis leading to significant lactate production, the pH microenvironment acidified, and falls in oxidative stress through the generation of reactive oxygen species, both situations ultimately promotes transcription of HIF1α.

Hypoxia-inducible factor-1 (HIF1) is a key regulator of the cellular response to hypoxia [2]. It is a heterodimer composed of constitutive, stable b subunits and unstable α subunits, which are synthesized yet, degraded under normoxic conditions due to the sequential action of oxygen-dependent prolyl hydroxylases (PHDs) and the VHL ubiquitin ligase (Figure 4). HIF1α functions as a transcriptional activator in hypoxia and binds specifically to the promoters or enhancers of more than 100 genes involved in multiple aspects of tumor biology [11] (Figure 5), including growth factors such as vascular endothelial growth factor (VEGF), which promotes angiogenesis; epidermal growth factor (EGF); insulin growth factor-2 (IGF-2); transforming growth factor beta (TGF-b), which stimulates growth and cell survival, moerever of glycolytic enzymes and glucose transporters. With regard to the contribution of HIF1α reprogramming of energy metabolism, it stimulates the conversion of glucose to pyruvate and lactate by upregulating glucose transporter (GLUT) isoform 1 (GLUT1), hexokinase (HK1 and HK2, which catalyze the initial step of glycolysis), and lactate dehydrogenase A (LDHA), as well as the lactate-extruding enzyme monocarboxylate transporter 4 (MCT4). In addition, HIF-1 decreases the conversion of pyruvate to acetyl-CoA by

pyruvate dehydrogenase (PDH). For this, HIF-1 transactivates the gene encoding PDH kinase 1 (PDK1), which inhibits PDH. Acetyl- CoA is normally fed to the TCA cycle, producing the electron donors NADH and FADH2, which donate electrons to the respiratory chain complexes I and II, respectively. Hence, by inhibiting PDH, HIF-1 compromises OXPHOS. In addition, HIF-1 counteracts the stimulatory action of Myc on mitochondrial biogenesis (Figure 2), thereby reducing mitochondrial mass. In this way HIF-1α is a promoter of tumor progression and start, making it a target drogable [2,11,12].

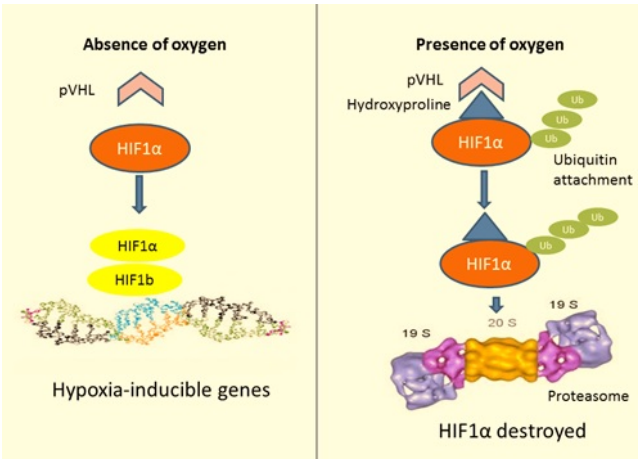

Figure 4: HIF1α physiology in the absence and presence of oxygen.

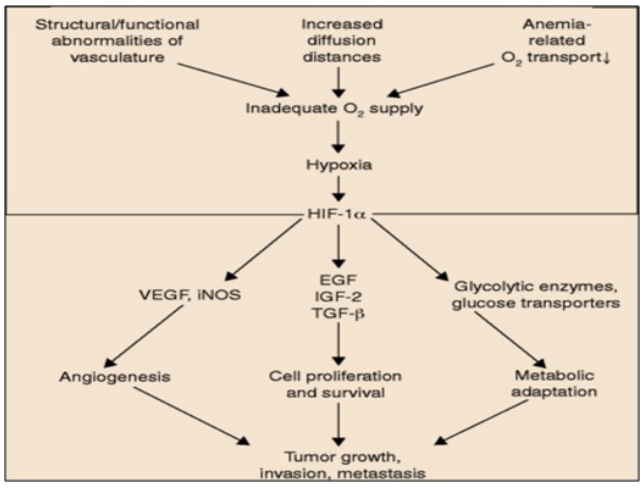

Figure 5: Link between HIF1α and cancer.

Even though multiple alterations in the nuclear-encoded genes such as tumor suppressor and oncogenes are believed to play a key role in tumorigenesis, the involvement of the mitochondrial genome to this event remains controversial to date. Mitochondrial DNA has been suspected to be associated with the carcinogenesis because of its high sensitivity to mutations and inefficient repair mechanisms in comparison to nuclear DNA [13].

The evidence demonstrating the existence of mtDNA mutations in several types of cancer are:

1. The first somatic mtDNA mutation was detected 15 years ago by Bert Vogelstein's group in human colorectal cancer cells [13].

2. Mohamed [13], in review about "Role of mitochondrial DNA mutations in brain tumors" inform that to date, according to Mitomap (http://www.mitomap.org), a mitochondrial genome database, more than 30 mutations and sequence variations in mtDNA associated with brain tumors have been reported. The most commonly mutated mtDNA locus in all brain tumors is the displacement loop (D-loop) region. Several types of somatic mtDNA alterations have been identified in brain tumors. These mtDNA alterations include point mutations, deletions, insertions, mitochondrial microsatellite instability, and copy number changes. Point mutations A number of studies have detected mtDNA point mutations in cancer of the brain and other CNS, including gliomas, astrocytomas, gliomatosis cerebri, medulloblastoma, meningiomas, schwannomas, and neurofibromas.

3. According Yadav et al. [10], studies performed in the last few years have characterized various alterations in mtDNA in breast cancer, including point mutations, mtDNA polymorphisms, mtDNA depletion, microsatellite instability, insertions, and changes in mtDNA copy number, homoplasmy, and heteroplasmy of mtDNA. Breast nipple aspirate fluid (NAF) with mtDNA mutations at position 204, 207, and 16293 has been suggested to be indicative of breast cancer and mtDNA D-loop mutation has also been proposed as an independent prognostic marker for breast cancer.

4. Lee et al. [14] observed a high frequency of alterations in the copy number of mtDNA and microsatellite instability (mtMSI) in samples of lung carcinoma and adenocarcinoma, and that mtMSI was more frequent in the more advanced stages of lung cancer. Thus concluding that mitochondrial DNA is a potential molecular marker in lung cancers (ADC and SCC) correlating with their histological classification.

But also mtDNA mutations or alterations have also been identified in bladder cancer, esophageal cancer, head and neck cancer, hepatocellular carcinoma, ovarian cancer, renal cancer, thyroid cancer, and a number of blood cancers [14-20].

Over-regulation of aerobic glycolysis as a result of oncogenic process

Activation or gain of function of oncogenes and loss of function of tumor suppressor genes are associated, by various mechanisms, reprogramming of tumor metabolism. Examples:

The constitutive activation of phosphatidylinositol 3-kinase (PI3K) phosphorylate AKT kinase resulting in an association of HK (hexokinase) con VDAC (voltage-dependent anion channel). This complex HK-VDAC stimulates the glycolysis, up-regulated the carriers of glucose and elevated the resistance to apoptosis [2].

It has been reported that activation of the c-Myc oncogene stimulates glycolysis and down-regulated OXPHOS [2]. In transformed cells, high levels of c-Myc promote energy production and biomolecule synthesis, which are required for rapid proliferation, independent of growth factor stimulation [21,22]. Similar to HIF, c-Myc enhances the glycolytic pathway by increasing target gene expression such, glucose transporters, pyruvate kinase, as well as lactate dehydrogenase A, thereby allowing efflux of glucose-derived

carbon as lactate [36]. Moreover, c-Myc drives anabolic pathways, with targets that include carbomyl phosphate synthetase, aspartate transcarbomylase, dihydroorotase and serinehydroxymethyl transferase, fatty acid synthase and ornithine decarboxylase [23-25]. Interestingly, c-Myc can collaborate with HIF to confer metabolic advantages to tumor cells. Although HIF-2a accentuates c-Myc-Max heterodimer-mediated transcriptional activation by stabilizing the c-Myc-Max complex, HIF-1a binds Max and renders c-Myc inactive when Myc is regulated at normal levels. In contrast to the physiological regulation of c-Myc by growth factor stimulation of normal cells, many cancers overexpress c-Myc. When c-Myc is highly increased, its activity is not affected by HIF-1a because the high levels of c-Myc protein maintain c-Myc-Max heterodimers through mass action. In this way, these transcription factors act in concert to reprogram metabolism, protein synthesis and cell cycle progression [26].

A shift toward glycolysis is further induced by HIF-1. It actively suppresses mitochondrial oxidative metabolism by increasing the expression of pyruvate dehydrogenase kinase 1 (PDK1), which phosphorylates and inactivates pyruvate dehydrogenase (PDH), the enzyme that converts pyruvate to acetyl-CoA for entry into the TCA cycle [27,28]. Also, HIF-1 activates the expression of lactate dehydrogenase A, which converts pyruvate to lactate, the end product of glycolysis [29]. To summarize, the activation of HIF-1 notably contributes to a shift in metabolic flux toward glycolysis by inducing expression of glucose transporters and most of the glycolytic enzymes (Figure 2).

Recent studies have demonstrated that many tumor-associated mutant p53 proteins, particularly these several "tumor hot-spot mutants", not only lose tumor suppressive functions of wild type p53 (wtp53), but also gain new oncogenic functions that are independent of wtp53, including promoting cell proliferation, anti-apoptosis and metastasis, which are defined as mutp53 gain-of-function (GOF). About this, in 2013, Zhang et al. [30] published a study which showed in vitro (cultured cells) and in vivo (mutp53 knock-in mice as a new mutp53 GOF), that tumor-associated mutant p53 (mutp53) stimulates the Warburg effect through promoting GLUT1 translocation to plasma membrane, which is mediated by the activated RhoA and its downstream effector ROCK, and that the inhibition of the RhoA/ROCK/GLUT1 signaling largely abolishes mutp53 GOF in stimulating the Warburg effect. About the same thing Kraemer et al. [2], and Soga [26], argue that inactivation of p53 can directly cause the Warburg phenomenon through several mechanisms, including expression of GLUT (GLUT 1, GLUT4 and GLUT3), enhancement of glycolysis enzymes (phosphofructokinase and phosphoglycerate mutase), suppression of mitochondrial respiration by inhibition of synthesis of cytochrome c oxidase 2 and glutaminase 2 (GLS2), and activation of AKT and HIF, which are effectors downstream of PI3K.

Both endothelial cells and tumor cells express the F1F0 ATPase (normally an inner mitochondrial membrane protein complex) at the cell surface, where it may extrude protons from the cytosol to the extracellular milieu and hence contribute to the net export of protons that is required to maintain aerobic glycolysis [2].

Final Thoughts

Recent studies have shown that metabolic changes are a hallmark of tumor cells and a key contributor to tumor development. Most tumor cells primarily utilize glycolysis for their energy needs even under normal oxygen concentrations, a phenomenon termed "the Warburg effect". It's characterized by a much higher rate of glucose uptake and higher lactate production in tumor cells compared with normal cells. The Warburg effect provides a rational for Positron Emission Tomography imaging developed for tumor detection since tumors take up more of the glucose analog 18 flurodeoxyglucose than normal tissues. Emerging evidence has indicated that the Warburg effect contributes greatly to tumorigenesis and could be targeted for tumor therapy [1,2]. However, the mechanism for the Warburg effect is not well-understood. According Yeung et al. [31], the underlying mechanisms leading to the Warburg phenomenon include mitochondrial changes, upregulation of rate-limiting enzymes/proteins in glycolysis and intracellular pH regulation, hypoxia-induced switch to anaerobic metabolism, and metabolic reprogramming after loss of p53 function. Soga [26] argues that three genes are essential for the reprogramming of energy metabolism in the cancer cell: P53, HIF, and c-Myc.

This review has established that aerobic glycolysis or Warburg phenomenon is a feature common to all tumors regardless of their race, constituting a key factor in tumor initiation and progression, as it can be a cause or a result of oncogenic process.

Conclusions

Reprogramming of energy metabolism is a hallmark of cancer, independent of its nature.

Metabolic reprogramming may be the consequence of non-metabolic oncogenic events. Thus, major oncogenic events (such as constitutive activation of growth factor pathways, constitutive activation of HIF-1, c-Myc, and inactivation of p53) may constitute the common cause of metabolic programming and well-studied hallmarks of cancer such as autonomous growth, resistance against apoptosis, limitless replication, and angiogenesis.

Aerobic glycolysis contributes to the promotion and/or exacerbation of oncogenic process mediating the upregulation of HIF-1 which activates the expression of target genes associated with tumor process.

HIF-1α is a key molecule for reprogramming of energy metabolism in the cancer cell, constituting a potential target drogable.

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