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Warburg Effect and its Role in Cancer Cell Metabolism: A Review

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Abstract: ***Elevated glycolysis and impaired oxidative phosphorylation (Warburg effect) is one of the classical features of cancer. Cancer cells, in order to support their growth and proliferation needs both high energy and more biosynthetic intermediates, therefore they alter their metabolic activities. However, high proliferation rate of tumor cells often generates regions that become oxygen deficient. Therefore, their carbohydrate metabolism depends mostly on a glycolytic process that is coupled with oxidative phosphorylation. This metabolic switch, also known as the "Warburg Effect", constitutes a fundamental adaptation of the tumor cells to a relatively hostile environment, and supports the evolution of aggressive and metastatic phenotypes. The glycolyic phenotype created due to Warburg Effect grants the cancer cells, in hypoxic conditions; a growth advantage by inducing various pro-proliferative and pro-invasive process like angiogenesis. This, tumor glycolysis may constitute an attractive target for cancer therapy. In this review, we discuss some of the mechanisms by which cancer cell metabolism may shape and modify the tumor microenvironment. Also, we will detail how two specific environmental factors present in the tumor microenvironment including hypoxia and acidosis, reciprocally affect cancer cell metabolism.***

Keywords: Tumor microenvironment, Glutaminolysis, Chronic acidosis, Tumor hypoxia

1. Introduction

1.1 Cancer and Warburg Effect

Cancer is a complex and multistep process that requires inhibition of several barriers such as senescence, programmed cell death-inducing mechanisms, and antiproliferative responses. This occurs mainly due to the mutations in tumor suppressor genes and oncogenes [1]. It has been shown that both genetic and environment factors contribute to the Warburg effect in tumor cells. The tumor microenvironment plays a vital role in transition from pre-cancerous lesion to carcinogenesis [2]. Cancer cells depend upon variety of metabolic fuels. Glucose is used as a fuel for most of the mammalian cells and is metabolized by Glycolysis, which is a multistep process leads to the formation of pyruvate. This pyruvate enters the mitochondria and is oxidized by Krebs Cycle to generate ATP in typical cells under normal oxygen level. Whereas, in cancer cells lactate is produced by orienting the pyruvate away from mitochondria *via* action of lactate dehydrogenase (LDH/LDHA). In normal cells this is usually occur in absence or low concentration of oxygen for example, during brisk exercise. This lactate production in the presence of oxygen is termed "aerobic Glycolysis" or the Warburg Effect first described by Otto Warburg in 1920s [3].Instead of oxidative phosphorylation, cancer cells preferentially utilize Glycolysis, even in the presence of oxygen [4]. Originally Warburg hypothesized that impairments of mitochondria lead to the defective irreversible respiration of cells that could cause that development of cancer [5].

1.2 Cancer Cell Metabolism

Studies on *c-Myc* oncogene demonstrated that c-Myc gene can increase the expression of genes involved in glycolysis, such as Glucose transporter 1 (GLUT1) and lactate dehydrogenase –A (LDH-A) and thus stimulate the glycolytic metabolism of cancer cells. Warburg effect is also regulated by environment factors found in tumor. Tumor hypoxia and acidosis which results from inadequate supply of oxygen (O_2) appears to be strongly associated with tumor propagation, malignant progression, and resistance to therapy [6, 7]. Acidosis has recently been shown to suppress glycolysis and augment mitochondrial respiration in cancer cells [8, 9]. In contrast it is well established that the hypoxia inducible factors (HIFs) mediate hypoxia enhances the Warburg effect by up-regulating glycolytic genes such as *hexokinases*, LDH-A and GLUT [10]. These observations illustrate close relation between tumor microenvironment and cancer cell metabolism

Hypoxia results from less oxygen supply to cells and an imbalance between oxygen supply and consumption. As tumor grows oxygen and nutrient delivery becomes less but the consumption by abnormally proliferating cancer cells increases that leads to the advancement of hypoxia. Hypoxia also leads to the production of an acidic environment. Tumor progression is the cancer hallmark which is coupled with hypoxia and acidosis. In hypoxic condition Glycolysis is upregulated, this glycolytic phenotype is not an efficient means for energy production by cancer cells [4]. In Oxidative phosphorylation 30 ATP from one glucose molecule are produced whereas Glycolysis produces two lactic acid and 2 ATP. Glycolysis is not energy sufficient and tumor cells should depend on oxidative phosphorylation. However, this is not true for cancer cells. Glycolysis plays an important role in the survival of cancer cells under hypoxic condition.

Tumor development is also dependent on the angiogenesis that is, formation of new blood vessels. These new blood vessels increase blood flow, nutrient deposition and thus lead further tumor growth [11]. Tumor associated endothelial cells (TECs), which grow from pre-existing blood vessels results in angiogenesis [12]. An important molecule involved in the adaptation of hypoxia is the hypoxia – induced factor 1 (HIF-1). HIF-1was first identified in1990s as a transcriptional factor which is activated when oxygenation reduced in cell [13]. HIF-1 is a heterodimer composed of two subunits, HIF-1α and HIF-1β. HIF-1 is stabilized by low oxygen availability. HIF-1 is

translocated to the nucleus where it regulates the expression of vascular endothelial growth factor (VEGF), which is a major pro-angiogenic factor.

Along with up-regulated Glycolysis, other molecular changes in cancer cells under hypoxia are mitochondrial selective autophagy, glucose-independent citrate production for fatty acid [14]. HIF-1 is the most defined of all the three isoforms of HIF that is, HIF-1, HIF-2 and HIF-3 in upregulating glucose metabolism to promote cell survival under hypoxia [15, 16]. Von Hippel-Lindau protein(pVHL) is a tumor suppressor gene which regulates HIF-1 alpha subunits whose stability is oxygen dependent [17, 18]. During normoxia or in the presence of oxygen, VHL spots E3 ligase complex which then recognizes HIF-α that has been subjected to prolyl hydroxylation [19]. Contrariwise during hypoxia, HIF omit degradation as VHL is unable to bind HIF-1α which leads to its stabilization.

Acidosis is one of the classical features of cancer cells microenvironment and it is dependent on blood perfusion and cancer cell glycolytic metabolism [2, 20, 21]. In cancer cells pH ranges from 5.5-7.4 as contrary to normal pH of 7.4 [2, 20]. High lactate accumulation in tumor interstitial space is one of the reasons for this drop in pH. This lactic acid is produced during anaerobic metabolism. Lactate and protons are exported from cancer cells by monocarboxylate transporters (MCT1), Na+/H+ exchangers, and other acid-base transporters [22, 23]. Due to defective blood perfusion and inefficient removal, protons and lactate accumulate in the tumor interstitial space. The Lactate accumulates in cancer cells because of defective perfusion of blood and faulty removal. Effects of acidosis can be viewed as acute *versus* chronic [24]. Decrease in cancer cell proliferation, stimulation of acidosis and cell cycle arrest may occur during acute acidosis whereas; somatic evolution of cancer cells is induced during chronic acidosis [25-28]. Chronic acidosis is the result of Darwin selection pressure. Chronic exposure to acidosis selects for acidosis resistant cancer cells which shows uncontrolled and high proliferation. Acidosis may act as a stimulator for immune cells, such as neutrophils in contrast acidosis may be functionally repressive in cells such as natural killer (NK) and $CD8^+$T lymphocytes [29-31]. Also, tumor pH may further reduce by respiratory bursts or increased oxygen consumption, in the presence of immune cells [32, 33]. Angiogenesis and vascular cell inflammation has also been shown to be affected by acidosis [34, 35]. Acidosis may alter tumor cell metabolism by various mechanisms. In short, we can say that the acidosis in the tumor microenvironment has multiple effects on cancer cells.

Acidosis and hypoxia can over express many inflammatory response genes like; tumor necrosis factor alpha (*TNF-α*). Genes related to unfolded protein response such as C/EBP homology *protein* (*CHOP*),activating transcription factor-3 (*ATF3*), activating transcription factor-4 (*ATF4*), and eukaryotic translation initiation factor 2-alpha (*eIF2α*) are also over expressive. ATF4 overexpression is advantageous for cells as it helps in tumor cell survival during endoplasmic (ER) stress and severe hypoxia. In some cases hypoxia and acidosis may oppose each other effects like, during treatment with acidosis expression of a specific subset of hypoxia related genes such as carbonic anhydrase 9 (*CA9*), phosphoglycerate kinase 1 (*PGK1*), and stanniocalcin 1 (*STC1*) is antagonized under hypoxia [36]. In acidosis, by inhibiting the translation of HIF1-α hypoxia induced genes can be down-regulated [36]. Also, p53 plays an important role in the metabolic response to acidosis. Acidosis activates p53 and induces TCA cycle by hindering Glycolysis. p53 expression which is induced under acidosis reduce availability of glucose for Glycolysis by inhibiting the expression of GLUT1 and GLUT4 (glucose transporters). Also, acidosis can increase glutaminolysis and direct glucose towards pentose phosphate pathway (PPP) by activating p53 and over expressing glucose 6 phosphate dehydrogenase (G6PD) [37, 38]. . Many cancer types have p53 mutations and these mutations play an important role in acidosis related cell death. In many tumor cells chronic acidosis related cell death has been linked with p53 loss-of-function mutation but, this is not always the case as cell death is not always dependent on p53 function. Through autophagy response, tumor cells may omit cell death [26, 39].

2. Cancer Therapy

2.1 Warburg effect and cancer therapy

The main culprit for hypoxic microenvironment of tumor cells is HIF-1. Hypoxia promotes angiogenesis and thus, helps tumor cells to proliferate. One of the strategies to treat cancer is to directly target HIF-1 or its target gene which regulate metabolism and angiogenesis. HIF-1α can be regulated for therapy and some of the approaches are, by inhibiting HIF-1α and DNA binding, HIF-1 translation, and HIF-1α degradation [40, 41]. Digoxin and acriflavine has been shown to block tumor growth and vascularization as it inhibits dimerization and synthesis of HIF-1. Trichostatin A (TSA) also degrade HIF-1α by inhibiting histone deacetylases [42]. Whereas Flavopiridol inhibits *HIF-1α*gene transcription and is under clinical trials [43-46]. Cyclin-dependent kinase inhibitor, P276-00 induces G2/M cell cycle arrest and thus, inhibits HIF-1α under hypoxia [47].

VEGF is important for angiogenesis as it is a HIF-1 target gene and can an ideal target for therapy as tumor much needed supply of oxygen and nutrients can be eliminated. Sunitinib, sorafenib and pazopanib are multi-targeted kinase inhibitors, approved by the FDA and are used to target multiple cancer types [48-50]. Currently, the most prevailing strategy in anti-angiogenesis therapy is VEGF blockage. Monoclonal antibody, Bevacizumab is under clinical trials for anti-angiogenesis therapy as it specifically targets VEGF [51]. VEGF targeting is a growing field of therapy but the benefits is short lived because tumor quickly recovers vascular growth through other compensatory pro-angiogenic signaling pathways [52].

2.2 Acidosis and cancer therapy

Throughout the growth of solid tumor, the tumor microenvironment can become acidic because of many reasons like accumulation of lactic acid and protons. Acidosis can be used as an effective therapy only if some of

the phenomenon can be taken into accounts before administration of chemotherapeutics like; the uptake of weakly basic drugs in tumors with low pH is reportedly reduced whereas weakly acidic drugs were taken up more readily [53-55]. Another problem is that the cytotoxicity of certain chemotherapeutical drugs such as cisplatin, teniposide, vincristine, and topotecan, among others may reduce in the tumor acidic microenvironment [53-55]. Advantage of acidosis can be taken as tumor microenviroment influence the uptake of certain drugs. Several nanoparticles, such as low pH insertion peptides (pHLIP) and polyethylene glycol (PEG) based hydrogels integrated with imidazole are being designed that are activated by acidic pH and release chemotherapeutic drugs [56-57]. G protein-coupled receptors (GPRs)also known as seven-transmembrane domain receptors are one of the largest family of membrane proteins. These receptors play an important role in many physiological processes like, immunity, inflammation. In many studies, it has been shown that GPR overexpression in cancer cells plays an important role in survival of cancer cells. GPR87, GPR68, GPR4, GPR 132 are seen to be overexpressed. Today more than 30% of all present drugs which are utilized and present in market target G-protein coupled receptor for the treatment of human diseases. In treatment for tumorigenesis also, GPR is targeted. For example, GPR87, which is a cell surface GPR related to LPA receptor family, is overexpressed in diverse cancers and helps tumor cell in its survival. p53 regulates GPR87 and absence of GPR87 triggers an increase in p53 and decrease in Akt, which push tumor cells to DNA damage-induced apoptosis and growth suppression. For this reason GPRs have been extensively used for drug development for carcinogenesis. This is undoubtedly a very promising target for cancer prevention and treatment [58].

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