Review

Hypoxia and cancer cell metabolism

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The past decade has witnessed a rapid accumulation of evidence showing that hypoxic microenvironment, which is typical during cancer development, plays key roles in regulating cancer cell metabolism. In this review, we will focus on the role of hypoxic response, particularly, its master regulator hypoxia-inducible factor-1, in regulating glucose, lipid, as well as amino acid metabolism in cancer cells. We will also discuss the therapeutic opportunities by targeting specific pathways that facilitate metabolic reprogramming in cancer cells.

Keywords  hypoxia; HIF-1; cancer; metabolism

Received: October 31, 2013 Accepted: December 3, 2013

Introduction

As one of the central characteristics for cancer development, low oxygen (O2) concentration, or hypoxia, often occurs in the center of solid tumors where vascular is often abnormal or limiting. In response to reduced O2 tension, hypoxia-inducible factor (HIF) is found activated to mediate the primary transcriptional adaption to hypoxic stress in cancer cells [1,2]. HIFs are composed of O2-regulated HIF-α subunit (HIF-1α, HIF-2α, and HIF-3α) and O2 independent continuously expressed HIF-1β subunit (ARNT). HIF-1α, HIF-2α, or HIF-3α dimerizes with HIF-1β through their basic helix-loop-helix domain to form a heterodimeric complex which can recognize and bind to hypoxia response elements (HREs) in the genome [3,4]. While HIF-1α is expressed ubiquitously in all cells, HIF-2α is only expressed in certain cell types such as endothelial cells. The expression profile and functions of HIF-3α are largely unknown. It has been well established that HIFs act as key transcriptional regulators orchestrating adaptation to hypoxic stress at tissue or cellular levels during homeostasis and diseases. Accumulating evidence suggested that HIFs are involved in regulation of angiogenesis, cell survival, proliferation, apoptosis, adhesion, and metabolism by transcriptionally activating downstream targets such as vascular endothelial growth factor and erythropoietin [5]. Hence, HIF pathway, HIF-1 in particular, plays important roles in tumor growth, and clinical data also proved that high expression of HIF-1α resulting from intratumoral hypoxia or genetic alterations is frequently associated with increased patient mortality for many types of cancers. In this review, we focus on the effects of hypoxia and HIF-1 on cancer cell metabolism. Particularly, we will discuss the molecular mechanisms as well as potential therapeutic strategies of the altered cancer cell metabolism regulated by hypoxic conditions.

HIF-1 and Warburg Effect

More than 80 years ago, Otto Warburg observed that cancer cells consumed much more glucose to produce lactic acid than normal cells even under sufficient O2 condition. This finding, named ‘aerobic glycolysis’ or ‘Warburg effect’, first interpreted the change of glucose metabolism in cancer cells. Warburg [6] believed that the defects of respiration caused metabolic disturbance which was important for tumorigenesis. After Warburg, many biologists tried to interpret the molecular basis of aerobic glycolysis occurred in cancer cells. Accumulated evidence suggested that many cancer genes, such as Ras, cMyc, and p53, are all involved in the regulation of Warburg effect [7]. As a master regulator of cancer hypoxic response, HIF-1 also plays very important roles in regulating aerobic glycolysis to meet the biosynthetic demands of cancer cells and to prevent cancer cells from damage of hypoxic stress [8].

HIF-1 increases glucose uptake and lactate production

As Warburg described, cancer cells shift from oxygen-dependent efficient ATP production via oxidative phosphorylation (OXPHOS) in mitochondria to the less efficient cytoplasmic glycolysis. As a result, tumor cells need to consume more glucose to maintain its energy requirements for growth and survival. It has been documented that HIF-1α activates the expression of glucose transporter 1, 3 (Glut1, Glut3) under hypoxic condition [9,10], which ensures sufficient glucose uptake by cancer cells. In addition, the expression of glycolytic enzymes including hexokinases (HK1 and
HK2) and phosphoglycerate kinase 1 (PGK1) are also induced by HIF-1α, leading to enhanced glucose flux in glycolysis [11,12]. At the last step of glycolysis, HIF-1α promotes lactate production and electron acceptor NADH generation by up-regulating lactate dehydrogenase A (LDHA) expression [13]. Thus, HIF-1 pathway facilitates cancer cell glycolysis, a low efficient but rapid method, to obtain energy by enhancing glucose uptake and increasing glycolytic enzyme activity. Recently, it has been demonstrated that glycolytic enzyme pyruvate kinase M2 (PKM2), one of the HIF-1α target gene, can regulate HIF-1α activity by enhancing its binding to HRE, eventually up-regulating HIF-1α target gene expression [14]. This working model points out a new feedforward mechanism that glycolytic enzymes, such as PKM2, can regulate HIF-1α transactivity [15].

**HIF-1 blocks tricarboxylic acid cycle and OXPHOS**

A well-recognized key event for cellular energy metabolism is that, under the sufficient oxygen condition, cells convert glucose step by step to pyruvate which is then catalyzed to acetyl-CoA by pyruvate dehydrogenase (PDH) complex and enters the mitochondrial tricarboxylic acid (TCA) cycle. However, during hypoxic condition, as often occurs in solid tumors, pyruvate dehydrogenase kinase isozyme 1 (PDK1) is activated by HIF-1α, which inhibits PDH activity by phosphorylating its serine residues at three different sites [16–18]. Therefore, HIF-1-induced PDK1 expression blocks the conversion of pyruvate to acetyl-CoA, as a result, preventing the ATP production via TCA cycle and OXPHOS in mitochondria. Since PDK1 can reduce reactive oxygen species (ROS) production in cells, HIF-1 pathway, thus, protects cell from ROS damage through PDK-1 induction under hypoxic stress. HIF-1 pathway also optimizes cancer cell respiration by regulating the switch of the subunits of cytochrome oxidase (COX-4) [19]. Moreover, HIF-1 induces miR-210 transcription, which decreases the expression of iron-sulfur cluster assembly proteins (ISCU) and cytochrome C oxidase assembly protein (COX10), two important elements of the mitochondria electron transport chain and the TCA cycle [20,21]. These results collectively demonstrated that HIF-1 reduces mitochondrial respiration under hypoxia condition, which inhibits the aberrant electron leakages from mitochondrial electron transport chain, thereby serving as a safeguard for tumor survival by preventing ROS production under hypoxic stress [22].

**HIF-1 regulates mitochondria biogenesis**

In addition to blocking TCA cycle and OXPHOS in mitochondrial, HIF-1 pathway also negatively regulates mitochondrial biogenesis itself. In one study, using renal clear cell carcinoma (RCC) cells where HIF-1α and HIF-2α proteins are constitutively expressed due to the dysfunction of von Hippel-Lindau (VHL) gene, mitochondrial mass, mitochondrial DNA content, and oxygen consumption are inhibited compared with cells with forced expression of wild-type VHL. Further study reveals that HIF pathway regulates mitochondrial biogenesis via suppression of PGC-1β through oncogene cMyc [23]. In another study using HIF-1α knock-out mouse embryonic fibroblast (MEF) cells, it was found that hypoxia leads to elimination of mitochondrial by inducing autophagy in an HIF-1-dependent pathway [24]. HIF-1 up-regulates BNIP3 expression under hypoxic condition, which leads to Beclin1-dependent mitochondrial autophagy and reduces mitochondrial mass and functions eventually in MEFs. Collectively, HIF-1 down-regulates mitochondrial biogenesis through different mechanisms including induction of mitochondrial autophagy, as a consequence, ROS production is decreased to benefit cancer cell survival in prolonged hypoxic condition which is often the case during cancer development.

**HIF-1 and Lipid Metabolism in Cancer Cells**

As with glucose metabolism, lipid metabolism is also altered in cancer cells [25,26]. For example, to meet the need for cell proliferation, tumors require more fatty acids for the synthesis of cellular membranes, energy storage, and signaling molecules than normal cells. Hypoxic cancer cells have its unique metabolic needs for lipids through HIF-dependent changes in metabolism.

**HIF-1 stimulates fatty acid synthesis and triglyceride storage**

Most cancer cells prefer choosing de novo synthesis of fatty acid to using them directly to maintain homeostasis of the essential materials for cell survival and proliferation [27,28]. Recently, hypoxia was proved to increase fatty acid synthesis by inducing sterol regulatory-element binding protein (SREBP)-1 activation and fatty acid synthase (FASN) expression in a HIF-1α-mediated pathway [29]. Furthermore, two recent reports showed that hypoxia promoted tumor growth by utilizing a novel reductive metabolism to synthesize acetyl-CoA for fatty acid synthesis [30,31]. These results shed light onto understanding why tumors favor de novo lipid synthesis. The excess lipid will, in turn, be used to form triglyceride and lipid droplets for storage. In this process, HIF-1α directly regulates phosphatidate phosphatase isofrom 1 (Lipin1), an essential enzymes that catalyzes triglyceride biosynthesis in the penultimate step, and hypoxia-inducible protein 2 (HIG2) which functions in lipid droplets accumulation on membranes [32,33]. Overall, these results showed that hypoxia can enhance fatty acid synthesis and triglyceride storage through an HIF-1α-dependent pathway in cancer cells.
Hypoxia reduces fatty acid oxidation

Fatty acid oxidation usually occurs in mitochondria where fatty acid substrate, acetyl-CoA, is catalyzed to produce acetyl-CoA and FADH. Now that hypoxia has been considered to decrease mitochondrial biogenesis and functions in cancer cells, it stands to reason that hypoxia might regulate fatty acid oxidation in tumors as well. One recent report revealed that carnitine palmitoyltransferase 1 (Cpt-1) and acetyl-CoA synthase long-chain family member 1 (Acs11), which facilitate fatty acid import and oxidation, respectively, were both suppressed by activation of HIF-2α in liver-specific VHL-knockout mouse model. In this model, as a critical regulator, HIF-2α increased hepatic lipid accumulation, impaired fatty acid oxidation and caused severe hepatic steatosis [34]. On the other hand, HIF-1α, not HIF-2α, was proved to be the major factor that regulates ventricular cell lipid accumulation [35]. However, the molecular mechanism underlying hypoxic regulation on fatty acid oxidation is still largely unknown.

HIF-1 and Amino Acid Metabolism in Cancer Cells

Glutamine, another major energy substrate besides glucose for cancer cell growth, has received much attention during past several years [36]. Cancer cells utilize glutamine for the synthesis of proteins, nucleotide, hexosamine, non-essential amino acids, glutathione, respiratory substrate, and reducing equivalents. These multi-functions of glutamine reflect its importance in cells not only as a nutrient substrate but also as a mediator of other biological processes [37]. It is now well recognized that HIF-1 plays a central role in many developmental events [45]. It is known that hypoxia enhances the survival of hematopoietic stem cells and prevents differentiation of human embryonic stem cells [46,47]. Moreover, hypoxia also promotes the generation of induced pluripotent stem cells, which was induced by four transcriptional factors, Oct4, Sox2, Klf4, and c-Myc [48,49]. Therefore, hypoxia and HIFs play critical roles under broad spectrum of homeostasis and diseased contexts. Hence, HIF dysregulation has been investigated in many disease models, such as coronary artery disease, peripheral arterial disease, hereditary erythrocytosis, and cancers [50].

Therapeutic Opportunities by Targeting HIF-1 and Cancer Metabolism

It is now well recognized that HIF-1 plays a central role in cancer cell energy metabolism and, more importantly, promotes cell survival by regulating a switch from OXPHOS to glycolysis under hypoxic conditions. In many cancers, aberrant expression and high activity of HIF-1 often lead to poor prognosis. Therefore, one of the promising therapeutic efforts is conceived to be the inhibition of HIF-1 or HIF-1-mediated cancer metabolic pathways that are essential for cancer cell survival under hypoxic conditions [5,51,52]. Many drugs, such as digoxin [53] and acriflavine [54], were found to block tumor growth by inhibiting HIF-1 expression or activity, providing potential new anti-cancer therapies. On the other hand, drugs that target HIF-1-mediated metabolic pathways such as endogenous glutamine synthesis and cell survival under hypoxia in rat pheochromocytoma cells. The importance of glucose-independent endogenous glutamine synthesis under hypoxia in rat pheochromocytoma cells. The importance of glucose-independent endogenous glutamine synthesis under hypoxia in rat pheochromocytoma cells.
enzymes could also affect the hypoxia-induced tumor malignancy. For example, two reports, respectively, suggested that the inhibition of LDHA [55] or PDK1 [56] expression will change the ability of cancer cells to metabolize pyruvate to lactate, leading to decreased tumor growth in vitro and in vivo. Moreover, dichloroacetate, a PDK1 chemical inhibitor, was tested in phase I/II clinical studies for treatment of glioma and glioblastoma multiforme [57].

With regard to fatty acid synthesis, cancer cells prefer de novo fatty acid synthesis, which is different from their normal counterparts. Moreover, in hypoxic stress, cancer cells enhance lipid synthesis that is important for membrane biosynthesis and energy storage for cell survival and proliferation. FASN, which is induced by hypoxia both in vitro and in vivo, mediates tumor de novo fatty acid synthesis. Furuta et al. [29] found that the inhibition of FASN expression could overcome hypoxia-induced chemoresistance in tumors. Other reports also showed the suppression of the FASN expression by chemical inhibitors, such as mycotoxin cerulenin, and β-lactone orlistat, could partially decrease the hypoxia-induced chemoresistance, preferentially kill cancer cells, and retard the tumor growth in xenografts models [58,59]. Those results provided a strategic rationale to block the tumor-specific fatty acid synthesis to treat cancers.

As we mentioned earlier, glutamine metabolism is essential for cancer cell proliferation under hypoxia and glucose restriction. As a result, specific therapy could be devised to target glutamine metabolism for cancer therapy. In fact, cancer cells become more sensitive to the bis-2-(5-phenylactamido-1,2,4-thialdiazol-2-yl)ethy sulfide, a GLS inhibitor, under the conditions [41]. At the same time, the biological availability of glutamine in the blood could be reduced by phenylacetate, a drug condensing with the γ-amino group of glutamine, leading to its excretion in urine. The drug seems not harmful to human beings [60].

Hypoxia-induced metabolic reprogramming in cancer cells is a complicated event which could not be simply elucidated as a shift from OXPHOS to aerobic glycolysis. HIF-1 pathway plays very important roles during this metabolic reprogramming in cancer cells. Combining HIF-1 inhibitors with the emerging compounds that target different metabolic pathways may provide new strategies for anti-cancer therapy.

**Concluding Remarks**

Cancer cells often change metabolic phenotype to adapt to the changes in their living environment. As one of the most common stresses during solid tumor formation, hypoxia,
largely via regulation of HIF-1, broadly influences the glucose, lipid, and amino acid metabolism in cancer cells (Fig. 1). For glucose metabolism, hypoxia blocks glucose entering into TCA cycle and switches energy production from OXPHOS to glycolysis, a less efficient but more rapid and safer method. Meanwhile, hypoxia also induces lipid synthesis for the membrane biosynthesis and energy storage for cell survival and proliferation. Since glucose is prevented to be converted to acetyl-CoA under hypoxia, utilization of glucose is enhanced in a reductive carboxylation pathway to sustain TCA cycle as well as lipid synthesis. We believe a more detailed dissection of cancer-specific metabolic alterations will advance our understanding of cancer development, leading to new approaches towards cancer therapy.

**Funding**

This work was supported in part by National Basic Key Research Program of China (2014CB910600 and 2012CB910104), National Natural Science Foundation of China (31171385 and 31371429), and the Fundamental Research Funds for the Central Universities in China. H.Z. is supported by Chinese Government ‘1000 Youth Talent Program’.

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