Cancer Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Hypoxia and hypoxia inducible factors in tumor metabolism

Wen Zeng [a,b], Peiyi Liu [a,c], Weimin Pan [d], Shree Ram Singh [e,1], Yiyong Wei [a,c,*]

[a] Shanghai Key Laboratory for Prevention and Treatment of Bone and Joint Diseases with Integrated Chinese-Western Medicine, Shanghai Institute of Traumatology and Orthopaedics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 20025, China
[b] Department of Joint and Bone Disease Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China
[c] Department of Orthopaedics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 20025, China
[d] Department of Human Movement Studies, Xi'an Physical Education University, Xi'an 710068, China
[e] Mouse Cancer Genetics Program, Center for Cancer Research, National Institutes of Health, National Cancer Institute, Frederick, MD 21702, USA

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Hypoxia
HIFs
Tumor
Metabolism
Tumor microenvironment
Apoptosis

ABSTRACT

Because of the abnormal vasculature, most growing solid tumors contain regions that experience either acute or chronic hypoxia. However, tumor cells can maintain a high glycolytic rate even when there is enough oxygen supply. Hypoxia-inducible factors (HIFs) play crucial role in the response of tumor cells to this distinct microenvironment by shifting energy production from mitochondria towards glycolysis. In this review, we focus on the metabolism of tumor cell survival in hypoxic microenvironments. Furthermore, we also emphasize the mechanisms by which hypoxia and HIFs regulate tumor metabolism.

Published by Elsevier Ireland Ltd.

1. Introduction

One of the most validated explanations for altered metabolism in tumors is the poorly formed tumor vasculature that exists within tumors [1]. Because of the rapid growth of tumor cells, significant regions of the tumors are located at a great distance from the supporting blood vessels [2]. The growth of tumor cells is typically limited to a region of approximately 10 cells of a blood vessel, which results in the formation of an oxygen and nutrient gradient that supplies the tumor [3]. Generally, tumor cells respond to these specific conditions and adjust their metabolism to adapt to this unusual microenvironment [4].

Important factors in the response of tumor cells to this distinct microenvironment are the activities of the hypoxia inducible factors (HIFs). The HIFs are essential for the maintenance of cellular oxygen homeostasis and hypoxia adaptation when oxygen levels are too low for the cell [5,6]. HIFs are associated with the PAS (Per-ARNT-Sim) family of basic helix-loop-helix transcription factors that bind as heterodimers to DNA. HIFs are composed of an oxygen-dependent α subunit and an oxygen-independent β subunit. The α subunit has three isoforms: HIF-1α, HIF-2α, and HIF-3α. The β subunit, which is also known as aryl hydrocarbon receptor nuclear translocator (ARNT), has only two isoforms HIF-1β and HIF-2β. The α-subunit is transported into the nucleus and dimerizes with the β subunit when oxygen concentrations is below 6% [7–9]. This complex binds to the core sequence 5-RCGTG-3 of hypoxia responsive element (HRE) within the enhancer promoter region of HIF target genes. HREs facilitate the transcription of target genes, which results in adaptation of tumors to the hypoxic state, including angiogenesis, anaerobic energy supply, metabolic regulation, pH balance, and cell apoptosis [10–13].

2. Characteristics of tumor metabolism

The citric acid cycle (or Krebs cycle) occurs in the mitochondrial matrix, a crucial components metabolic pathway, where most of the aerobic organisms generate chemical energy in the form of adenosine triphosphate (ATP), which is derived from the catabolism of glucose, fats, and proteins into CO_2. This cycle also supplies precursors for the synthesis of some amino acids and reduces nicotinamide adenine dinucleotide (NAD+) to NADH for specific biochemical reactions [14,15].

Cellular metabolism within solid tumors has been known for many years to be significantly different from normal tissue. Cells in the solid tumor with size more than 1 mm^3 contain hypoxic

* Corresponding author at: Shanghai Key Laboratory for Prevention and Treatment of Bone and Joint Diseases with Integrated Chinese-Western Medicine, Shanghai Institute of Traumatology and Orthopaedics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 20025, China. Tel.: +86 21 64370045.

E-mail addresses: singhshr@mail.nih.gov (S.R. Singh), dr.yiyongwei@yahoo.com (Y. Wei).

[1] Co-corresponding author at: Mouse Cancer Genetics Program, Center for Cancer Research, National Institutes of Health, National Cancer Institute, Frederick, MD 21702, USA. Tel.: +1 301 846 7331.

http://dx.doi.org/10.1016/j.canlet.2014.01.032
0304-3835/Published by Elsevier Ireland Ltd.

stress because of the slower blood vessel growth [16]. A shift in cellular metabolism from mitochondrial respiration to glycolysis is linked with tumor malignancy. Recently, increasing attention has been paid in identifying the changes in glucose metabolism in cancer cells to allow for a shift away from mitochondrial respiration towards anaerobic glycolysis for the production of ATP [17]. An adequate oxygen supply may prevent glycolysis because glucose consumption is usually proportional to the availability of oxygen in normal tissues. In contrast, tumor cells that grow normal oxygen tension display elevated rates of glycolysis that meet most of their energy needs even though their supply of oxygen is normal. This phenomenon has been defined as the Warburg effect [18,19]. A key regulator of this process is thought to be involved in the stabilization of HIF-1α, which activates the transcription of genes that encode glucose transporters and other glycolytic enzymes, such as lactate dehydrogenase A (LDHA), phosphoglycerate kinase 1 (PGK-1), and hexokinase 1 (HK1) [19,20], Fig. 1. HIF-1α therefore plays a vital role in the glycolytic switch [17].

3. The effects of HIF regulation on glucose metabolism in cancer cells

Cellular metabolism within solid tumors is known to be significantly different from normal tissue [20]. In normal tissue, approximately 10% of the cell's energy is generated by glycolysis, whereas mitochondrial aerobic respiration accounts for the other 90%. However, in tumor tissues, more than 50% of cellular energy is generated by glycolysis and the other parts are produced in mitochondria [2]. Interestingly, this switch is maintained even when there is enough O_2 present to maintain mitochondrial function. This phenomenon has been termed "aerobic glycolysis" [18,21]. Because of the low efficiency of glycolysis in the generation of ATP, the dependence of tumor cells on glycolysis for energy production causes these cells to consume more glucose.

Tumor cells continue to show elevated rates of glycolysis even they are grown under normoxic conditions that correlate with the increased expression of glycolytic enzymes and glucose transporters, this could be due to the activation of HIF-1α. It has been shown that HIF-1α regulates the switch from pyruvate catabolism and oxidative phosphorylation to glycolysis in both hypoxic and normoxic cells [22]. In addition, many of the genes that are regulated by HIF-1α are linked with glucose metabolism [23–25]. In fact, HIF-1α directly stimulates glycolysis by activating the expression of glucose transporters and glycolytic enzymes. Further, HIF-1α also prevents mitochondrial oxidative phosphorylation by blocking pyruvate entry and the changing of pyruvate to acetyl-CoA. This HIF-1α-dependent pathway stimulates glycolysis and inhibits mitochondrial O_2 consumption thereby promoting tumor cell survival, even in acute and prolonged hypoxic conditions.

Oncogenes have also been shown to promote glycolysis in the tumor microenvironment [25–28]. Most glycolytic enzymes contain evolutionarily conserved, consensus Myc-binding sites within their regulatory DNA sequences. The Myc oncogene can bind to these promoters and transactivate LDH type A (LDH-A) expression, which converts pyruvate to lactate and promotes glycolysis under normoxic conditions [29]. Independently of HIF-1, AKT binds tightly to the mitochondrial membrane, induces glucose transporters, and functions as a glycolytic enzyme that can activate glycolysis without an increase in oxidative phosphorylation [30]. Another important transcriptional regulator of tumor metabolism is p53, which is one of the most frequently mutated genes in cancer cells [31]. The p53 protein represses the transcriptional activity of the Glucose transporter 1 (GLUT1) and Glucose transporter 3 (GLUT3) gene promoters by direct DNA binding, which leads to a decrease in glucose uptake and controls the balance between oxidative respiration and glycolysis.

4. The effects of HIF regulation in lipid metabolism in cancer cells

Although the Warburg effect has been recognized since the 1920s, little attention has been paid to lipid metabolism. In

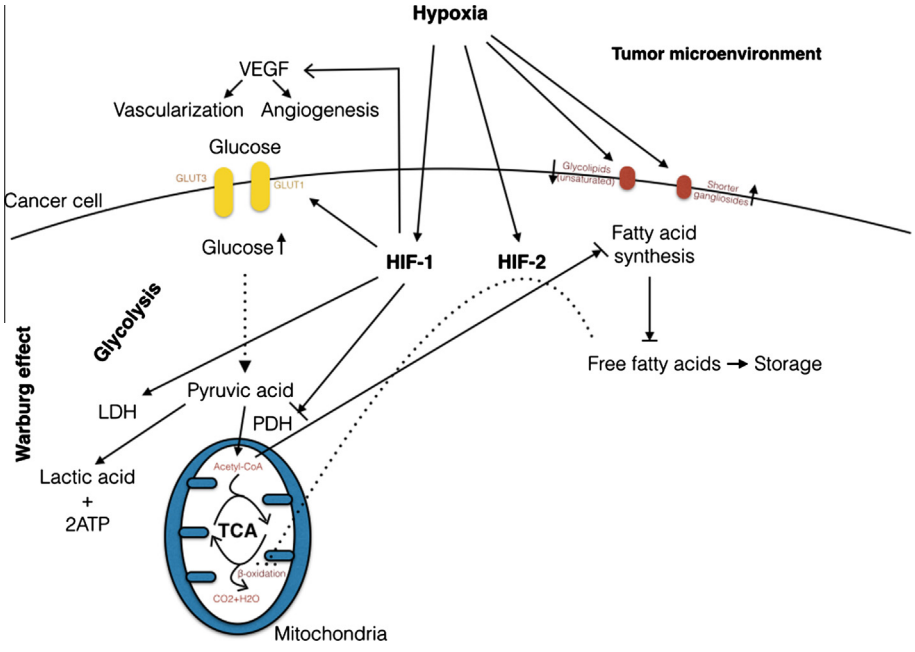

Fig. 1. Molecular basis of hypoxia on tumor metabolism: with the rapid growth of the tumors and the limited to the angiogenesis that result in an oxygen and nutrient gradient in tumor microenvironment. HIFs play a vital role in the tumor metabolism. HIF-1 affects the process of angiogenesis and vascularization by promoting VEGF expression in tumor tissue. HIF-1 also promotes the glucose levels by the activation of glucose transporter GLUT-1, GLUT-3 in tumor cells. HIF-1 can further promote glycolysis by the activation of LDH and suppression of PDH, and this process was named Warburg effect. HIF-2 inhibits the synthesis of fatty acid and the produce of free fatty acid, and promotes the fatty acid storage finally. HIF-2 can also control the expression a wide variety of surface glycolipid including unsaturated glycolipids and shorter gangliosides related to the surface marker of the tumor.

Please cite this article in press as: W. Zeng et al., Hypoxia and hypoxia inducible factors in tumor metabolism, Cancer Lett. (2014), http://dx.doi.org/10.1016/j.canlet.2014.01.032