Effects of hypoxia on tumor metabolism

Jung-whan Kim · Ping Gao · Chi V. Dang

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Abstract Rapidly growing tumors invariably contain hypoxic regions. Adaptive response to hypoxia through angiogenesis, enhanced glucose metabolism and diminished but optimized mitochondrial respiration confers survival and growth advantage to hypoxic tumor cells. In this review, the roles of hypoxia, the hypoxia inducible factors, oncogenes and tumor suppressors in metabolic adaptation of tumors are discussed. These new insights into hypoxic metabolic alterations in tumors will hopefully lead us to target tumor bioenergetics for the treatment of cancers.

Keywords Tumor · Hypoxia · Hypoxia-inducible factor · Metabolism · Tumor bioenergetic

1 Introduction

Ever since the build up of earth’s atmospheric oxygen, organisms have adapted and utilize oxygen for the efficient generation of energy through mitochondrial oxidative phosphorylation. It is intriguing that multicellular organisms have also preserved an ability to adapt to low oxygen conditions or hypoxia, which existed in earth’s infancy [1]. Low oxygen supply is frequently inevitable under physiological as well as pathological conditions. The dependence of mammals on oxygen for cellular energy production necessitates an efficient, adaptive cellular response to hypoxia including metabolic alteration, angiogenesis and erythropoiesis. A number of studies have verified that hypoxia-inducible factors (HIFs) mediate this critical adaptation [2]. In addition, hypoxic cells also activate non-HIF-mediated mechanisms for adaptation to hypoxic microenvironment (Fig. 1).

The vascular system develops in an organism to deliver and distribute oxygen and nutrients to normal tissues. Solid tumors arise without an existing vascular system, and hence could only exist by recruiting new blood vessels that are invariably inadequate and dysfunctional, leaving most tumor beds hypoxic. A number of studies have demonstrated a link between hypoxia, tumor progression and clinical outcomes [3, 4]. In this review, recent advances in delineating molecular mechanisms underlying tumor metabolic alterations including hypoxic HIF-dependent and independent pathways as well as non-hypoxic cell autonomous pathways will be discussed.

2 Hypoxia-inducible factor-1 (HIF-1) and tumor metabolism

2.1 Hypoxia and HIF-1

The tumor hypoxic microenvironment, resulting from inadequate and disordered neo-vasculature, selects for tumor cells that could respond and adapt to oxygen deficiency. The hypoxia-inducible factor-1 (HIF-1) permits tumor cells to adapt by inducing hypoxia responsive genes
HIF-1 is a heterodimeric transcription factor consisting of two subunits, a constitutively stable β subunit and an oxygen sensitive α subunit [8]. In non-hypoxic conditions, oxygen-dependent post-translational hydroxylation of two proline residues (402 and 564) of HIF-1 α subunit is mediated by three enzymes, prolyl hydroxylase 1–3 (PHD 1–3), with PHD2 playing a critical role [9–11]. Hydroxylated HIF-1α is then recognized by von Hippel Lindau (vHL) tumor suppressor protein, an E3 ligase, followed by ubiquitination and proteasomal degradation [12–14]. Under hypoxic conditions, however, reactive oxygen species-mediated inactivation of PHD results in stabilization of HIF-1α, which heterodimerizes with β subunit, translocates into nucleus and transactivates its target genes such as those encoding glucose transporters, enzymes in glycolytic pathway, erythropoietin and vascular endothelial growth factor (VEGF) [5, 6, 15, 16].

2.2 HIF-1 and human cancers

Earlier studies using immunohistochemistry of human tumor sections demonstrated that HIF-1 is prevalent in various types of solid tumors [4, 8, 17]. In most cases, increased HIF-1 expression clearly correlates with poor clinical outcomes: high mortality rate, poor response to radiation and chemotherapy, and metastasis. In support of a role for HIF-1 in tumor progression, genetic or pharmacological inhibition of HIF-1 in animal model systems manifests decrease in tumorigenesis and increase in survival [15, 18]. However, in certain tumors, HIF-1 expression appears to be associated with higher apoptotic rates and decreased