Function and expression of prolyl hydroxylase 3 in cancers

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Abstract

Hypoxia inducible factor (HIF) is a product of tumor cells that plays an important role in protecting tumor cells and adjusting to low oxygen tension through driving the progression and aggressiveness of tumors and changing the growth, angiogenesis, differentiation and metastasis of tumors. Prolyl hydroxylase 3 (PHD3) is a member of PHDs that are induced in hypoxia. Many studies have shown that PHD3 not only can hydroxylate HIF-1α, but also has various other biological functions. Thus PHD3 plays significant roles in suppressing the growth, angiogenesis, differentiation and metastasis of tumors and promoting apoptosis of tumors under hypoxic conditions. It may become a new tumor suppressor gene and also may become a new approach to investigate tumors.

Key words: prolyl hydroxylase 3, cancer, hypoxia inducible factors.

Introduction

Prolyl hydroxylase 3 (PHD3) is one of the important molecules expressed under hypoxic conditions. Scientists from different countries have found that PHD3 plays significant roles in suppressing tumors and promoting apoptosis of tumors, when they investigated the occurrence of cancers and their therapy. Under hypoxic conditions, PHD3 has been shown to be positively expressed. In recent years, studies have further confirmed that PHD3 plays an important role in cancer chemotherapy and radiotherapy. The specific role of PHD3 in tumor development and treatment is not very clear. In this paper we review PHD3's functions in the pathogenesis of tumors and inhibiting tumor cell growth and the role of cancer chemotherapy.

When the human body is challenged with low oxygen tensions, it mounts a wide-ranging adaptive response involving cellular and systemic processes. A lot of solid tumors are composed of large regions of poorly perfused cells, resulting in areas of low oxygen (hypoxia) throughout the cell mass. Cells in response to hypoxia exhibit a complex set of responses that change their metabolism, rebalance their survival mechanisms, increase their invasive capacity and stimulate angiogenesis [1]. All of that allows them to temporarily escape the nutrient starvation at least and cell death in this poor environment. The hypoxic regions are often the sources of the most aggressive and therapy-resistant cells in tumors, and there-

fore those cells drive tumorigenesis. Hypoxia, the reduction in oxygen availability, is a universal stimulus to which most organisms are subjected during their life. With the development of humans, it became a positive stimulus, which could promote vascular development and change cell phenotype [2]. However, hypoxia can also result in pathogenic responses, such as the ischemia and reperfusion injury sustained in stroke or myocardial infarction or the tumorigenic responses found in cancer [3, 4]. Hypoxia is a strongly selective pressure that often drives the progression and aggressiveness of tumors [4]. It is found in most, if not all, solid tumors and results in changing cellular phenotype, including alterations in gene expression, governing metabolism, migration or invasion, survival, proliferation, and differentiation [5, 6]. Many of the alterations in gene expression under hypoxia are mediated by heterodimeric transcription factors known as hypoxia inducible factors (HIFs) [1].

The HIF is considered to be a transcriptional activator of cells to adapt to the hypoxic environment [7]. More than 100 HIF regulated genes have been identified; they play important roles in physiological processes, including vasomotor control, angiogenesis, erythropoiesis, iron metabolism, cell proliferation/death, and energy metabolism [8]. The HIFs are composed of a constitutively present β subunit and a hypoxia-stabilized α subunit [9]. There are three α subunits: HIF-1α and 2α heterodimerize with HIF-β to form the HIF-1 and HIF-2 transcription factors, whereas HIF-3α is of unknown function [10]. The HIF-α subunits are labile under normoxic conditions due to the actions of PHD enzymes [11]. These enzymes form a family of α-ketoglutarate-dependent dioxygenases, which are members of a superfamily of nonheme iron dioxygenase enzymes [12]. The HIF-1 complex binds hypoxia responsive elements to activate downstream genes that benefit tumor survival [4]. High levels of HIF-1α have been identified in many types of human cancer [13], such as breast cancer. There is evidence showing that HIF-1α plays a crucial role in tumor behavior [13].

The HIF plays a central role in this process, inducing transcriptional targets that enhance oxygen delivery, promote adaptation of cells to hypoxia, or modulate cell proliferation or survival pathways [14, 15]. Both HIF-1 and HIF-2 transcription factors play a critical role in tumor adaptation to hypoxia through activation of genes involved in angiogenesis, anaerobic glycolysis, and adaptation to acidic pH and modification of these factors by prolyl hydroxylation followed by VHL-mediated degradation may provide the critical tool in manipulating HIFs stability [16]. Hypoxia may, under different circumstances, either promote or protect cells from apoptosis, and HIF itself contributes to these processes both indirectly, through the defense of cellular energy supplies, and directly via transcriptional changes in proapoptotic or prosurvival genes. However, to generate the anatomical and physiological integrity required for oxygen homeostasis in the intact organism, these adaptive responses to hypoxia must be accurately interfaced with the developmental control of growth. The HIFs is also recognized as one of the most important microenvironmental influences on tumor behavior that enables tumors to acquire an aggressive phenotype and become resistant to both chemotherapy and radiotherapy [4]. The HIFs signaling is critically important for cell survival [17] in low-oxygen environments, as occur in tumors [18].

The HIF-1α is the best characterized PHD target that orchestrates many of the cellular responses to hypoxia in tumors. The HIF-1α is then able to translocate to the nucleus, where it dimerizes with its constitutively expressed partner HIF-1β and then binds to the hypoxic response element of genes that enhance tumor cell survival such as glycolysis (Glut1), angiogenesis, iron metabolism, pH control and hemoglobin synthesis [1]. In mammalian tissues, there are three PHDs that are coded by the EGLN1-3 genes. To date, three PHD isozymes have been identified and characterized (PHD1, PHD2 and PHD3) [11]. PHD1, PHD2 and PHD3 differ in their tissue distribution and their relative contributions to cellular capacity for HIF-α hydroxylation [19]. PHD1 was detectable exclusively in the nucleus, whereas the majority of PHD2 and factor inhibiting HIF (FIH-1) were found in the cytoplasm. The PHD3 was distributed more evenly in the cytoplasm and nucleus [20]. All PHDs can express a variety of unknown function mRNA due to different alternative splicing or translational initiation [21, 22]. The C-terminal which has the hydroxylase area is relatively conserved during evolution, but the N-terminal tends to be active [23]. In normal tissue oxygen concentration, the oxygen molecules and iron help PHDs to hydroxylate two conserved proline residues on HIF-α. The hydroxylated HIF-α quickly undergoes poly-ubiquitination with pVHL protein, then is degraded by the 26S proteasome [24]. All PHDs may have similar roles in some biological events, but they also have specific functions. The resultant decrease in PHD1 could result in responding via HIF-independent mechanisms in a tumor. Loss of PHD1 may downregulate cyclin D1 levels and suppress mammary tumor proliferation [25].

In addition to having a pivotal role in HIF degradation, PHDs have various other biological functions and functions as tumor suppressors [26]. For instance, using xenografted colon carcinoma with decreased PHD2 expression in mice, Chan *et al.* observed that tumors grew dramatically faster than the control group and that PHD2 loss also induced

angiogenesis and recruitment of bone marrow-derived cells [27]. In pancreatic cancer, Su *et al.* recently reported that PHD3 overexpression mediated tumor cell growth and invasion [28]. Overexpression of PHD1 was shown by Erez *et al.* to inhibit tumor growth [29]. Thus, overexpression of PHD1 suppresses tumor growth, and loss of PHD2 and PHD3 is associated with development of cancer. Some mutations of PHD2 have been previously reported in erythrocytosis and endometrial tumors [30] that decreased HIF binding, hydroxylase and inhibitory activities, which demonstrates the importance of PHD 2 in regulating HIF-1α activity. The PHD2 and PHD3 expression is modulated directly by hypoxia, PHD2 and PHD3 genes contain the hypoxia response element and can be activated by HIF-1α in hypoxia [31], but it is less appreciated that PHD1 levels may be altered through suppression of its mRNA under hypoxia. The PHD3 may also promote cell death through apoptosis [32].

The PHDs themselves have previously been shown to regulate some hypoxia responses, including apoptosis, in a HIF-independent manner [33]. Dales has previously shown that PHDs can be reactivated under hypoxia and result in a metabolic defect, both *in vitro* and *in vivo*, and esterify α-ketoglutarate, which will induce apoptosis and inhibit tumor growth, *in vivo*. The effects are independent of HIF-1α but dependent on the presence of PHD3.

The PHD3 not only has the above-referenced common functions of PHDs as one of the parts of PHDs, but also plays a particular role in the human body. The PHD3 is undetectable or expressed at a low level in normoxic cancer cells [34]. The expression is strongly induced during hypoxia. However, in hypoxia PHD3 remains mostly inactive and the full activity is restored upon reoxygenation. The PHD3 forms proteasome component-containing bodies that closely resemble aggresome-like structures and the activation of the PHD3-induced protein aggregation is strictly dependent on sufficient oxygen availability and, moreover, requires the hydroxylase activity of PHD3 [34]. Several lines of evidence imply that the abilities of PHD3 to trigger or induce apoptosis and to form aggresome-like structures are crucial biological mechanisms of the oxygen-sensing pathway to regulate cell fate. Cancer cells are resistant to reoxygenation-induced cell death and with the rapid oxygen-induced degradation of PHD3 in these cells and hydroxylation through PHDs enables binding with von Hippel-Lindau (VHL) tumor suppression protein with subsequent targeting of HIF-α for proteosomal degradation by ubiquitination [34]. Rantanen *et al*. also have observed that PHD3 polymeric protein could induce tumor cell apoptosis through transfecting the PHD3 gene into HeLa cells in the normal oxygen concentration [34].

The function of PHD3 in different cancers

In pancreatic cancer

Gossage found that the expression of PHD3 was positive in 32% of pancreatic adenocarcinoma via using immunohistochemical methods to detect pancreatic biliary tumor [35]. The study of Su *et al.* also found that the overexpression of PHD3 induced apoptosis in pancreatic cancer cells and inhibited tumor cell growth and infiltration [28]. The high PHD3 expression was significantly correlated with poor overall survival in pancreatobiliary ampullary adenocarcinoma [35]. Couvelard *et al.* found that high nuclear staining of PHD1 and PHD3 and stromal staining of FIH *et al*. were associated with worse survival in pancreatic endocrine tumors [36].

In gastric cancer

Su *et al*. found that the positive expression rate of PHD3 was 42.2% but not detected in non-cancerous mucosa and increased significantly from non-cancerous mucosa to cancer via studying 101 tissue samples in gastric cancer patients [37].

In colorectal cancer

In colorectal cancer tissues the expression of PHD3 is decreased and the low expression of PHD3 is associated with higher tumor grade and metastasis. The degradation of PHD3 increased the resistance of colorectal cancer cells to tumor necrosis factor α and tumorigenesis. In colorectal cancer cells PHD3 seems to be a tumor suppressor that acts via inhibiting the IKKβ/NF-κB signaling path, regardless of its hydroxylase activity. Activation of NF-κB has been observed in colon cancer. In colorectal tumors determination of PHD3 status could facilitate targeted therapy for patients who have increased activity of NF-κB [38].

In lung cancer

Compared with adjacent normal tissue the expression of PHDs was much higher in lung cancer tissue. In non-small cell lung cancer (NSCLC) the high expression of PHD3 was correlated with an early tumor stage and better differentiation. Moreover, the high expression of PHD3 was significantly correlated with the low expression of Bcl-2, which showed its potent ability in inducing apoptosis [39].

In breast cancer

Xu *et al*. has shown that body mass index, benign breast disease, older age of menarche and menopause were associated with high risk of breast cancer among Chinese women [40]. Fox *et al.* also have found that the positive expression of PHD3 rose from 39% to 45.6% in 211 cases of breast can-

cer patients after treatment with epirubicin and tamoxifen or dual-drug treatment [41]. Peurala *et al.* have observed that though the expression of PHD3 has no effect on HIF-1α downregulation, HIF-1α expression had a tendency for decreasing breast cancer-specific survival in breast cancer. The expression of PHD3 decreased with a high degree of malignancy and high growth, and PHD3 may be an important regulator of apoptosis that mainly is found in tumors with good prognosis [42]. Moreover, Fox *et al.* observed that the frequent expression of PHDs in invasive breast carcinoma ranged from 25% to 50% of cancer cells, suggesting that the PHDs are important in human breast cancer [41].

In head and neck squamous cell carcinoma

Bishop *et al.* found that PHD regulated neuronal apoptosis *in vitro* and *in vivo* studies [43]. Upregulation of PHD3 in head and neck squamous cell carcinoma (HNSCC) is indispensable for cell survival in a hypoxic environment through permitting promotion of cell cycle progression from G1 to S phase. Moreover, Högel *et al.* detected strong PHD3 mRNA expression in tumors of HNSCC [44]. A study demonstrated that PHD3 mRNA level was increased in different anatomical sites including tongue, mouth floor and tonsils [45]. Increased PHD3 expression under hypoxia enhances cell cycle progression and survival of carcinoma cells [46].

In renal cell carcinoma

Tanaka *et al.* found that PHD3 was overexpressed in 21 of the 22 renal cell carcinoma (RCC) specimens through RT-PCR analysis and anti-PHD3 antibody may be a novel serological marker for RCC [47]. PHD3 is mainly overexpressed in RCCs, but rarely in normal tissues and was recognized as a cancer-specific antigen and might be a target in immunotherapy for RCC [48].

In glioblastoma

The mRNA expression levels of PHD1-3 varied in protecting against hypoxia-induced cell death in glioblastoma. PHD3 is hypoxia-inducible in humans and one of the biological functions of PHD3 is the control of hypoxia-induced cell death via the regulation of HIF in glioblastoma [49].

Conclusions

Taking the evidence together, we can see that hypoxia can promote the progression and aggressiveness of tumors through HIF. In response to hypoxia, organisms produce PHD3 that hydroxylates HIF to suppress the progression and aggressiveness of tumors. The PHD3 may become a new target of tumor therapy and a major determinant of the clinical response.

Acknowledgments

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