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REVIEW

HYPOXIA AND CANCER

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Abstract

Hypoxia can be defined as the master regulator of the tumorigenesis process which can negatively affect the body response to radio- and chemotherapy. Solid tumors are characterized by hypoxia, with O_2 concentration around 0.1-1%. Hypoxia-inducible factors, especially HIF-1α are overexpressed in many human pathologies, including various types of cancer, chronic kidney disease, cardiovascular disorders, and age-related macular degeneration. Currently, three isoforms of HIF, HIF-1, HIF-2, and HIF-3 have been identified. HIF-1α is overexpressed in many cancer types, involved in initiation and progression, and correlated with a poor survival rate. The main aim of this review is to present the role of hypoxia during cancer progression.

Keywords: *hypoxia, solid tumors, isoforms, overexpression, survival rate*

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Introduction

Worldwide, cancer is the second cause of mortality (1). The study of the role of hypoxia in radiotherapy resistance of solid tumors began 71 years ago. Today, it is well known that hypoxia is a common feature of many cancers (2). Hypoxia is the master regulator of tumorigenesis processes, including angiogenesis, proliferation, metabolism, metastasis, and differentiation. Furthermore, hypoxia can negatively influence the body response to radiation therapy (2).

Malignant tumors are complex pathologies, their development being, characterized by three phases: initiation, promotion, and progression, respectively. Inflammation and oxidative stress (OS) are involved in the development of the first two steps. Moreover, during cancer evolution, many WNT/β-catenin target genes, including *c-Myc, cyclin D1*, and *hypoxia-inducible factor 1-alpha* (HIF-1α) are activated (3). Reactive oxygen species

(ROS) stimulate the production of Nuclear factor-kappaB (NF-κB) that further will lead to the synthesis of inflammatory factors, such as tumor necrosis factor -alfa (TNF-α), transforming growth factor-beta (TGF-β), interleukine-6 (IL-6), IL-8, matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX2), B-cell lymphoma-2 (Bcl-2), and inducible nitric oxide synthase. ROS may activate HIF-1α (3).

Solid tumors are characterized by hypoxia and necrosis (4). Depending on O_2 concentration, normoxia is characterized by ~21% O_2, physoxia ~1–13% O_2, and hypoxia has the lowest O2 value ~0.1–1% O_2 (5). The transition between acute hypoxia to chronic hypoxia is specific to tumor cells. Due to lack of oxygen, tumor cells become necrotic (4). Hypoxia is abundantly installed in tumors' core, leading to high proliferation rates of cancer cells, correlated with abnormal vasculature. Additionally, the most salient response to hypoxia is the induction of the growth factor hormone, erythropoietin (EPO) (5). In addition, hypoxia negatively affects the results of radiotherapy and chemotherapy, enhancing the potential of tumor metastasis (4).

Under hypoxic conditions, cells respond as follows: (a) inhibition of cell proliferation in order to prevent cells from consuming O_2; (b) reduction of oxidative phosphorylation rate; (c) enhancing the anaerobic glycolysis to decrease O_2 consumption per cell; (d) increased production of angiogenic factors (6). To survive the hypoxic conditions, tumor cells adapt to hypoxia by orchestrating various processes (7).

HIF and tumorigenesis

Studies performed on *C. elegans* to test HIF-1α roles on lifespan revealed that ROS and Krebs cycle metabolites stabilize the HIF-1α protein. In contrast, epidermal knockout of HIF-1α protein leads to keratinocytes apoptosis and wound healing delay (8). Moreover, in cultured fibroblast, loss of HIF-1α enhances cellular senescence (8). However, many studies reported that HIF-1α overexpression is correlated with many pathologies such as chronic kidney disease, interstitial fibrosis, cardiovascular disorders (atherosclerosis, cardiomyopathy, aneurysms) and even neovascularization in age-related macular degeneration (8). Moreover, ROS detected at tumor site are implicated in HIF-1 signaling (9).

HIF-1 is a heterodimeric protein that contains two subunits, the labile alpha unit (HIF-1α) and the stable form beta (HIF-1β) (10). The *HIF-1α* gene is located on chromosome 14q21-24; this gene may suffer various mutations and polymorphisms (11). The C1772T polymorphism is characterized by the substitution of proline with serine at codon 582, while G1790A corresponds to alanine substitution with threonine at codon 588 (11). Studies performed so far reported that C1772T

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polymorphism increase the risk of developing various cancer types such as glioma, cervical, endometrial, and pancreatic cancer. This polymorphism is not associated with liver, oral, or esophageal cancer (11).

Three isoforms of HIF, HIF-1, HIF-2, and HIF-3 have been discovered (12). HIF-1 is a heterodimer compound composed of two subunits, α and β (13). While HIF-1β is constitutively expressed, HIF-1α is rapid degraded under oxygen presence (13). Unfortunately, cancer progression and chemoresistance is correlated with tumor hypoxia and elevated HIF-1α expression (13). HIF subunits have distinct places in the genome, as well as distinct functions. HIF-1α promotes acute response to hypoxia, the second subunit 2α is involved in chronic response, while the last one, 3α seems to activate gene expression (14).

Moreover, during cancer development, an intricate regulation between miRNAs and HIF-1α have been discovered. This regulation modulates proliferation, metastasis, apoptosis, and drug resistance of cancer cells (15). miRNAs are small noncoding RNAs that act as negative regulators of mRNAs. Furthermore, at transcriptional level, miRNAs can be regulated by HIF-1α. On the other hand, HIF-1α itself can be modulated by many miRNAs (15). HIF-1α alterations have been observed during tumorigenesis, with the formation of a reciprocal regulation network (15).

Around 1.0-1.5% of the genome is transcriptionally regulated by hypoxia. HIF-1α is the main transcription factor that modulates a wide variety of genes related with anaerobic glycolysis, inhibition of fatty acid β-oxidation, production of ROS, and tumor suppressors (16). HIF-1 can promote selective mitochondrial autophagy, resistance to T cell that mediates cancer cells lysis, and pluripotent cancer stem cells activation (16). In addition, HIF-1 mediates the epithelial-mesenchymal and epithelial-mesenchymal-endothelial (EMT) transitions, which are important for tumor growth and progression, and even loss of E-cadherin (16).

HIF-1 is involved in many important processes such as angiogenesis, glucose metabolism, cell proliferation, survival, invasion, metabolic reprogramming, EMT, and metastasis. In human cancers, accumulations of intratumoral hypoxia and genetic mutations, lead to HIF-1α overexpression. In addition, HIF-1α overexpression is correlated with treatment failure and increased mortality (17).

HIF-1 is the master regulator of the hypoxic transcriptional responses (18). Therefore, hypoxia plays a key role in cancer initiation and progression, by the production of the transcriptional alfa helix factor. In normal conditions, prolyl hydroxylase enzymes (EGLN 1-3, or PHD 1-3) inactivate HIF by hydroxylation. When HIF is activated by EGLN, it can bind to Von Hippel Lindau protein (VHL), leading to its

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degradation (12), by proteasomal pathway (13).

Beside hydroxylation, HIF-α stability can be affected by acetylation, a mechanism that is poorly understood. HIF-α has 12 amino acid residues that can suffer post-translational modifications and depending on which residues are acetylated, the HIF-1 subunit stability may decrease or increase. In addition, in chronic hypoxia, acetylation of HIF-1α may enhance its' stability and transcriptional activity. For example, HIF-1α, but not HIF-2α, undergoes acetylation at the Lys site, which increases HIF-1α stability (19).

While HIF1 is expressed ubiquitously, HIF2 is expressed in various cell types such as vascular endothelial, lung type II pneumocytes, liver parenchyma, interstitial cells in the kidney, and stem cells. HIF 2 is stabilized at higher concentrations of O_2. Elevated levels of HIF in tumors are correlated with chemotherapy and radiation resistance and may exhibit enhanced proliferation and migration of tumor cells (20).

O_2-independent pathways such as phosphatidylinositol-3-kinase (PI3K) /protein kinase B/mammalian target of rapamycin (mTOR), growth factors and cytokines activate HIF-1α. In the presence of O_2, HIF-1α suffers degradation by ubiquitin-proteasomal pathway. The degradation process involves hydroxylation reactions at proline residues catalyzed by prolyl hydroxylases (PHDs). The hydroxylated products are further recognized by the von Hippel–Lindau (VHL) tumor suppressor protein that triggers its proteasomal degradation (18). Therefore, glycolysis in cancer cells has a great impact in cancer management, including diagnosis, treatment, and interaction with diabetes mellitus. Drugs targeting energy metabolism have a great impact on cancer treatment (21).

HIF-1α is overexpressed in many cancer types such as ovary, breast, uterus, cervix and oropharynx, its overexpression being correlated with a poor survival rate. Furthermore, HIF-1α is linked to AKT phosphorylation, so the axis AKT- HIF-1α-VEGF pathway contributes to tumorigenesis and angiogenesis in gastric cancer. Even if HIF-1α is frequently associated with poor prognosis in the case of gastric cancer patients, conflicting results are reported (22).

In cancer, it is well known that HIF-1 acts as a potent angiogenic factor promoting neovascularization (23). Wang Y and his research team examined the role of HIF-1α and HIF-2α regarding the invasiveness and metastasis processes in gastric cancer patients. Their results revealed that HIF-1α and HIF-2α were significantly correlated with the clinical stage and were increased in metastatic gastric cancers patients *versus* the control group (24).

Insulin-like growth factor (IGF), human epidermal growth factor (EGF), and prostaglandin E2 activate HIF-1α pathway. Moreover, PI3K/AKT pathway activates HIF-1α through mTOR. HIF-1α can be

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stabilized by reactive oxygen species and nitric oxide, leading to protein accumulation. Factors such as VHL, phosphatase, tension homolog deleted on chromosome 10 (PTEN) and p53 in cancer cells impair HIF-1α degradation or may increase its synthesis (25). In addition, beside PI3K/AKT, the extracellular signal-regulated kinase (ERK) pathway is also involved in HIF-1α expression and activity (26,27).

When HIF-1α enters the cells, at the nucleus level, the HIF1 complex is formed after the dimerization with HIF-1β. The resulting complex acts as a transcriptional factor for a huge number of genes, including those involved in angiogenesis such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and angiopoeitin-1 (ANGPT1) (28). Moreover, the HIF1 complex stimulates the synthesis of aldolase A and pyruvate kinase, enzymes which play a pivotal role in cell survival under hypoxic conditions (28). Acute hypoxia activates angiogenesis, apoptosis, or cell cycle arrest via HIF-1α transcriptional program. When the hypoxia becomes chronic, HIF-1α isoforms are switched to HIF-2α, which will enhance tumor adaptation, growth, invasion, and metastasis (28). Both HIF-1α and HIF-2α are correlated with tumor development, metastasis and promote EMT. While HIF-2α is expressed in certain cell types of vertebrate species, HIF-1α is expressed in most metazoan species. Furthermore, HIF-1α is involved in the apoptosis and the proliferation of non-small cell lung cancers (NSCLCs) (26). The hypoxic region is formed when malignant tumors proliferate very quickly. In colorectal cancer (CRC), HIF-1α expression is abnormally elevated and plays an important role in its' malignant progression (29).

Most cancer types (90%) are solid tumors that destroy the normal tissues and produce microenvironment lesions and further microenvironment tumor (TME) development. TME is associated with invasiveness, neovascularization, and drug resistance (30). In almost all cases of solid TMEs, tumor cells induce hypoxia. To sustain growth under hypoxic conditions, tumors upregulate angiogenic signaling by VEGF which increases tumor vascularization. Moreover, hypoxia induces changes in gene expression, leading to cellular and physiological alterations, correlated with a poor survival rate (30). For example, many metastatic breast cancer patients develop treatment resistance because of tumor hypoxia and the hypoxia inducible transcription factors (HIFs) (31). Beside angiogenesis, hypoxia can stimulate lymphangiogenesis (32). HIF-1α activation under hypoxic conditions is correlated, in tumor cells, with anaerobic metabolism, inflammation, vascular homeostasis, and tumorigenesis (33). TME is characterized by anaerobic glycolysis with production of lactic acid, which will trigger a decreased extracellular pH. In addition, HIF-1α activates the gene for carbonic anhydrase (CA). In tumor cells, CA catalyzes the reversible conversion of carbon dioxide to

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anion bicarbonate and proton, and therefore neutralizing the acidic medium. The human body has 15CA isoforms, where only CAIX and CAXII may be targets of CA inhibitors (34). The IX isoform overexpression is present in various tumors and is correlated with poor survival and progression. Therefore, CA inhibitors are used in glaucoma therapy, epilepsy, anti-infective treatment, and certain types of cancers (34). Copper and Zinc levels in plasma, have a positive effect on HIF-1α, leading to a decreased expression of VEGF, mitogenesis and angiogenesis (35).

In patients diagnosed with lung cancer and bone metastasis, osteolytic destruction is elevated, while osteoblastic activity is reduced. This suggests that hypoxia may play an important role in the process, but the exact mechanism is still unknown (36). In clinical trials of renal cell carcinoma, small inhibitors that bind to HIF-2α to block dimerization with HIF-1β are used (37). The study conducted by Mir R and his research team that included patients with breast cancer, reported that the HIF-1α gene genotype was correlated with different clinicopathological characteristics of breast cancer. The study observed that HIF-1α polymorphism was significantly associated with the distant metastasis in breast cancer patients *versus* the healthy group (38).

Liu T and co-workers investigated HIF-1α and p53 in non-melanoma skin patients. The research group detected that the mRNA expression levels for HIF-1α and p53 in tissues of patients with cancer were significantly elevated compared with the control group. Moreover, the levels of HIF-2α expression were linked to a good survival rate in some cancers, including B-cell lymphoma, lung adenocarcinoma, multiple myeloma, and breast cancer. The study concluded that vitamin B3 deficiency had a negative impact on patients with skin cancer, regarding the expression of HIF-1α and p53 (39).

Chang HL and colleagues detected, in 40 samples of human lung cancer, high levels of *HIF-1α-^{ex14}* transcripts that encode HIF-1αS isoform, compared with normal tissues and non-cancerous cells (40). The meta-analysis conducted by Han S and his research team investigated the expression of HIF-2α protein in patients with CRC. The study reported that HIF-2α was overexpressed in male compared with female diagnosed with CRC. Moreover, the meta-analysis observed that in CRC patients, HIF-2α expression was not linked with overall survival (OS), disease-specific survival (DSS), metastasis-free survival, and relapse-free survival. Also, the research group did not find any significant correlations between HIF-2α and OS or disease-free survival (DFS) in CRC patients. The meta-analysis also detected that the expression of both HIF-2α and VEGF (VEGFA, VEGFB, or VEGFC) were associated with a CRC poor metastasis-free survival rate (41).

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Conclusions

Hypoxia is installed in tumors' core being associated with increased rates of cancer cell proliferations. During cancer development, hypoxia orchestrates key processes: EMT, glucose metabolism, inflammation, angiogenesis, invasion, metastasis, radio- and chemotherapy resistance. Clinical studies performed so far reported that HIF-1α is overexpressed in various solid tumors correlated with a poor survival rate. In conclusion, tumor hypoxia can be regarded as an important target in cancer treatment.

Conflict of interest

The authors declare no conflict of interest.

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