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Review Article

Advances In the Study of Hypoxia Inducible Factors and Prognosis of Hepatocellular Carcinoma Development

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Abstract

Hypoxia-inducible factors (HIF) plays a major role in the regulation of hypoxia. It occurs not only under normal physiological conditions but also under pathological conditions such as some inflammatory reactions and tumor diseases. Studies have shown that the mechanisms of hepatocarcinogenesis include cellular molecules signaling pathways and gene levels in which Hypoxia-inducible factors play an important role. At present, surgical resection liver transplantation and chemotherapy are still the main treatment methods in the clinical treatment of patients with liver cancer but conventional chemotherapy drugs have toxic side effects on human body and the prognosis is poor. HIF is not only involved in reducing the efficacy of radiotherapy chemotherapy and targeted therapy but also closely related to angiogenesis and immune escape. In this article, we will focus on the Hypoxia-inducible factors of liver cancer and discuss its relationship with the development and prognosis of liver cancer and provide new ideas for the precise treatment of malignant liver tumors.

Keywords: hypoxia inducible factor; hypoxia; hepatocellular tumour

Introduction

Hypoxia is a key hallmark of solid tumors, involving enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis, and solid tumors often contain regions that suffer from acute or chronic hypoxia, but with varying severity in patients within and between tumor types [1]. Although prolonged and severe hypoxia is disadvantageous, cancer cells can survive and proliferate in this environment after adapting to the hypoxic microenvironment. Because the structural and functional abnormalities of tumor vasculature promote the development of tumor hypoxia, cancer improves its ability to grow in oxygen demand [2] by constantly adapting to the cancer vasculature. Hypoxia-inducible factor-1 (HIF-1) is present in mammalian cells cultured under hypoxic conditions and is required for enhancer-mediated transcriptional activation of the erythropoietin gene in hypoxic cells. Both subunits of HIF-1 are PAS domain-containing basic-helix-loop-helix proteins, defined by its presence in the Per and Sim proteins of Drosophila and the Arnt and AHR proteins of mammals. HIF-LCA is most closely related to SIM1, and HIF-1.3 is a series of Arnt gene products that can heterodimerize with HIF-1a or AHR. HIF-BX and HIF-113 (Arnt) RNA and protein levels were induced in cells exposed to 1% oxygen and rapidly declined after cells returned to 20% oxygen, consistent with a role for HIF-1 as a mediator of the hypoxic transcriptional response [3].

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related death worldwide. According to the American Cancer Society (ACS) 2020 statistics, the 5-year survival rate of HCC patients is 18%. Compared with the past, the growth rate of its case fatality rate has declined in both male and female patients [4]. At present, surgical resection, liver transplantation and chemotherapy are still the main methods of clinical treatment for patients with liver cancer [5], but conventional chemotherapy drugs have toxic side effects on human body and poor prognosis. HIF is not only involved in reducing the efficacy of radiotherapy, chemotherapy and targeted therapy, but also closely related to angiogenesis and immune escape. Therefore, the translational therapy targeting HIF may provide a new idea for the precise treatment of malignant tumors. Hypoxia leads to cellular responses that improve oxygenation and viability by inducing angiogenesis, increasing glycolysis, and changing metabolism by upregulating genes involved in cell survival/apoptosis [6]. Under hypoxic conditions, the driver factor HIF can regulate the expression of downstream genes through a variety of mechanisms, promoting tumor cell proliferation, tumor angiogenesis, EMT, and immune escape. Furthermore, it makes tumor cells more tolerant to hypoxic

microenvironment and acquire stronger proliferation, metastasis and invasion ability [7].

2. Hypoxia-inducible factor (HIF) and development of hepatocellular carcinoma

2.1 HIF is involved in fibrogenesis

The negative regulation of oxygen homeostasis is capable of affecting cells and tissues throughout the organism. The cellular response to hypoxia is characterized by the activation of multiple genes involved in many biological processes, with hypoxia-inducible factor (HIF) representing the master regulator of the hypoxia response. The active heterodimeric complex HIFα/β binds to the hypoxia response element (HRE), which determines the induction of at least 100 target genes to restore tissue homeostasis, and there is growing evidence that hypoxia signaling can act by generating contrasting responses in cells and tissues [8]. Salvi et al. [9] have described the role of HIF1-alpha in the progression of fibrosis in chronic liver disease. In hepatocytes, specific deletion of HIF1-alpha protects against liver fibrosis. Moczydlowska et al. [10] further demonstrated that transcriptional activation of HIF1-α is essential for the establishment and progression of liver fibrosis. Another study has shown [11] that induction of genes involved in epithelial-mesenchymal transition (EMT) is another way in which HIF1-alpha contributes to the progression of liver fibrosis. Some papers also suggest that HIF can play a role in attenuating liver fibrosis or liver regeneration. Shad et al. [12] used a rat model of liver regeneration to show that hypoxia can accelerate liver regeneration. In addition, Wang et al. [13] demonstrated that VHL overexpression can down-regulate fibrosis genes by affecting HIF-α stability, thereby reducing liver inflammation and fibrosis.

2.2 HIF and angiogenesis

In tumors, rapid cell proliferation is associated with hypoxic regions, hypoxia appears to promote tumor growth by inducing angiogenesis and activating anaerobic metabolism to promote cell survival, and the hypoxic response depends primarily on HIF-1 [14]. Duscher D et al. [15] generated and validated fibroblast-specific HIF-1α knockout mice in an experiment to understand the cell-specific hypoxic response to skin ischemia, suggesting that fibroblast expression of HIF-1α may affect cell survival and severely mediate angiogenesis in ischemic tissues. VEGF expression is reduced in the skin, and fibroblast expression of VEGF is thought to be critical in mediating vascularization and matrix formation. In the context of cancer [16-18], the mechanism by which HIF-1α loss in fibroblasts leads to impaired wound healing may be related to decreased VEGF signaling that affects normal vascularized granulation tissue formation. The findings highlight the importance of HIF-1α in regulating the transcriptional profile of fibroblasts during the vascular response to ischemia. Yosuke Watanabe et al. [19] have shown that increased levels of GSH adducts in ischemic muscle promote angiogenesis, the underlying mechanism of which can be explained by multiple targets of S-glutathionylation, which mediates angiogenesis during ischemia. It May be mainly due to the increase of angiogenic transcription factors, the decrease of sFlt1, the anti-angiogenic factor of HIF-1α, the activation of endoplasmic reticulum Ca2 + pump, and the inhibition of SERCA and phosphatase. S-glutathionylation increases active VEGFa by stabilizing HIF-1α and inhibiting the anti-angiogenic factor sFlt1, and enhances VEGFa signaling in endothelial cells by inhibiting PTP and activating SERCA2.

2.3 Involvement of HIF in cell survival

Cancer cells have been shown to have an altered metabolism compared to normal, non-malignant cells. The Warburg effect describes the phenomenon whereby cancer cells preferentially metabolize glucose via glycolysis to produce lactate as the end product despite the presence of oxygen. By providing the biological requirements for cell growth, the biochemical aspects of the Warburg effect provide a powerful explanation for why cancer cells proliferate. Pathways such as phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) and hypoxia-inducible factor-1 (HIF-1) are central regulators of glycolysis, cancer metabolism and cancer cell proliferation, and HIF-1 activation is associated with angiogenesis, erythropoiesis, and regulation of key enzymes involved in aerobic glycolysis. Thereby regulating a key process [20] required for the Warburg effect. Hypoxia-inducible factor (HIF) -1α is involved in tumor cell migration and invasion, and studies have reported a close relationship between VEGF overexpression, tumor progression, and adverse clinical outcomes. By targeting CAB39, miRNA-451 may inhibit the HIF-1α pathway to suppress tumor proliferation and invasion. Upregulation of miR-451 expression inhibits the growth and invasion of tumor cells in vitro and in vivo by targeting CAB39 and regulating HIF-1α signaling [21]. MiR-21 and miR-10b are associated with cell proliferation, apoptosis, and invasion by targeting tumor suppressor genes in a variety of human cancers [22-23]. It has been reported that both miR-21 and miR-10b contain an HRE region and can be induced by pH-dependent nucleolar sequestration of HIF1α and HIF-2α and vonHippel-Lindau (VHL) proteins [24-25]. Xiao-Peng Tian et al. [26] studied the function of exosomal miR-21 and miR-10b in regulating the progression of HCC, and found that the acidic microenvironment could clearly induce the expression of exosomal miR-21 and miR-10b in HIF-1α and HIF-HCC in a 2α-dependent manner. Knockdown of miR-21 and miR-10b resulted in decreased exosomal levels and significantly reduced HCC cell proliferation, migration, and/or invasion, whereas restoration of miR-21 and miR-10b by knockdown of HIF-1α and HIF-2α largely rescued HCC cell proliferation, migration, and invasion in vivo and in vitro.

2.4 HIF and immune escape

Exposure of cancer cells to reduced oxygen availability induces the activity of hypoxia-inducible factor (HIF).To produce a primary tumor, tumor recurrence, or metastatic tumor, cancer cells must possess two important characteristics: first, the cells must be protected from destruction by the immune system, and second, the cells must have stem cell properties. Hypoxia induces a cancer stem cell (CSC) phenotype [27-28] through the functional and physical interaction of HIF-1 with the coactivator TAZ and the HIF-dependent expression of pluripotent factors. Hypoxia also induces immune evasion [29-30] through several HIF-dependent mechanisms. The primary mechanism by which cancer cells evade the innate immune system is the expression of CD47, a cell surface protein that interacts with signal regulatory protein α (SIRPα) on the surface of macrophages to block phagocytosis [31-32] . Calreticulin (CRT) expression on the surface of cancer cells is a major trigger of phagocytosis [33] by binding to low-density lipoprotein-related protein (LRP) on the surface of macrophages. Phagocytic signals triggered by CRT-LRP ligation were counteracted by antiphagocytic signals triggered by CD47-SIRPα ligation [34]. When cancer cells are exposed to hypoxia, CD47 expression is induced in a HIF-dependent manner. Moderate inhibition of CD47 expression was sufficient to increase phagocytosis by cancer cells. It has been reported that increased expression of CD47 enables cancer cells to escape phagocytosis by macrophages and promote cancer stem cell phenotypes, and that hypoxia-inducible factor 1 (HIF-1) directly activates genes in CD47 transcriptional hypoxic cancer cells. Inhibition of HIF activity or CD47 expression increases phagocytosis of cancer cells by bone marrow-derived macrophages. Uncontrolled cell

proliferation and abnormal blood vessel formation lead to hypoxia in the cancerous area. Hypoxia-inducible factor (HIF) stimulates the expression of genes that cause cancer cells to invade and metastasize, leading to the death of patients. HIF is reported to stimulate the production of CD47, a protein on the surface of cells that allows cancer cells to avoid being destroyed by macrophages. CD47 is also important for maintaining cancer stem cells, a small subset of cells needed to form primary tumors and metastases [35].

2.5 HIF participation in targeted therapy

Strategies targeting HIF-1 levels have therapeutic potential in HCC because they may interrupt multiple pathways involved in angiogenesis, tumor metabolism, invasion, and survival. Down-regulation of the HIF-1 complex has been investigated by activating hydroxylase, by inhibiting HIF-1α binding to co-activators, and by small molecule inhibitors. In addition, small-molecule inhibitors such as topoisomerase inhibitor topotecan have been reported to negatively affect ribosome entry on HIF-1α mRNA, thereby preventing translation of the protein [36]. Another Avenue of research has been the development of HIF-1α mRNA antagonists. SPC2968, a HIF1α mRNA antagonist, is a locked nucleic acid (LNA) antisense oligonucleotide that down-regulates HIF-1α mRNA and protein. LNA oligonucleotides represent a new class of nucleic acid analogs in which conformational changes in the chemical structure result in higher affinity for mRNA and higher down-regulation potency. The drug is already in phase I trials in advanced malignancies to determine the maximum tolerated dose and dose-limiting toxicity. Although reduction in tumor size was noted, there was no correlation with clinical efficacy. The therapeutic potential of HIF-1α targeted therapy also lies in the possibility of combining treatment with other targeted therapies to improve efficacy and prevent drug resistance. For example, HIF-1α inhibitors can be used in combination with drugs that target the MAPK-RAF-ERK pathway, such as sorafenib and regorafenib. Liang et al. [37] reported the ability to overcome intratumoral hypoxia-associated sorafenib resistance by treating HCC cells with EF24, which results in VHL-dependent HIF-1α degradation and NF-κB inactivation. HIF-1 inhibitors, in combination with mTOR inhibitors that act upstream of HIF-1α, such as everolimus, may also down-regulate HIF1α synthesis and attenuate downstream signaling. Given the regulatory role of HIF-1α in the apoptotic pathway, combination therapy with a Stat3 inhibitor, upregulation of p53 expression (downstream of HIF-1α, or with a BCL2 inhibitor (also downstream of p53), would increase cancer cell apoptosis and enhance the effect of HIF-1 α inhibition. HIF-1α inhibition, particularly in combination with other therapies, is a promising area of research with the potential to help further advance the systemic treatment of HCC [38].

2.6 Prognosis of HIF treatment

HIF-1 is a major oncogenic factor in HCC, and related studies have shown that nitric oxide mimics GTN or 8-bromo-cGMP can prevent the accumulation of HIF-1α protein, block hypoxia-induced PD-L1 upregulation and further inhibit hypoxia-induced resistance of B16-OVA cells to CTL-mediated lysis [39]. In addition, inhibition of HIF-1 has been used to treat cancer [40-41]. Therefore, novel combination therapies that target tumor hypoxia by using HIF-1α inhibitors in combination with PD-L1 blockers may enhance the immune system of cancer patients. The results showed that the co-overexpression of PD-L1 and HIF-1α was an independent prognostic factor for OS and DFS, and the co-overexpression group had the worst prognosis. It was speculated that patients with co-overexpression of PD-L1 and HIF-1α might be more suitable for combined PD-L1/HIF-1 inhibition therapy [42]. Jia et al [43] studied the expression levels of serum HIF-1α and VEGF in HCC patients before and after TACE, and the correlation between prognostic factors and serum HIF-1α and VEGF levels. Forty consecutive HCC patients undergoing TACE were enrolled in the study. Studies have shown that the expression levels of HIF-1α and VEGF in HCC patients are significantly higher than those in controls. The serum levels of HIF-1α and VEGF reached the peak on the 1st day after TA CE. One week after TACE, their expression levels decreased, but were still significantly higher than those before TACE. One month after TA CE, the levels of HIF-1α and VEGF in CR group were significantly lower than those in PR + SD + PD group. There are few reports about the changes of HIF-1α and VEGF protein expression in HCC patients after TACE. Xiao et al. [44] performed immunohistochemical staining on specimens from 79 HCC patients who underwent surgical resection after TACE and 57 HCC patients who underwent surgical resection without TACE to detect changes in VEGF protein expression. The results showed that the positive rate of VEGF in patients with simple surgical resection was significantly lower than that in patients treated with TACE before surgical resection. HIF1α and VEGF, as effective factors of tumor angiogenesis, play an important role in the occurrence, progression and metastasis of HCC, and are of great significance in the evaluation of TACE efficacy and the formulation of individualized treatment for HCC patients. Monitoring changes in serum HIF-1α and VEGF levels or HIF-1α and VEGF protein expression in tumor tissue after TACE as part of the efficacy evaluation criteria enhances the evaluation of HCC treatment.

3. Conclusion

Many studies have highlighted the complex metabolic reprogramming that occurs in cancer cells that often face hypoxia. HIF is a transcriptional complex that acts as a primary sensor of oxygen levels through oxygen-sensing PHD enzymes. HIF controls myriad cellular functions, including proliferation and metabolism, in a PHD-mediated manner. We emphasize the importance of the HIF-1 system in the metabolic adaptation of cancer cells to hypoxia, a process that is essential for promoting cancer cell survival, proliferation, and metastasis. Thus, significant progress has been made in understanding the role of HIF-1 in cancer cells as a master regulator of cancer progression and as a potential target for cancer therapy. However, different aspects of HIF membership need to be clarified. For example, the interaction of HIF-1α with other family members (HIF-2α and HIF-3α) during hypoxic adaptation and the specific role of each family member. Understanding the regulatory mechanisms is important for identifying specific therapeutic targets. Closely related to HIF, targeting hypoxia is a potential therapeutic approach to deal with the progression of various cancers and allow long-term survival of patients.

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