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Mini Review

Emerging Roles of Hypoxia-Inducible Factor and Glucose Metabolism in Esophageal Cancer: Possible Targets of Cancer

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Abstract

Hypoxia-Inducible Factors (HIFs) are important nuclear transcription factors that are activated in solid tumors, such as esophageal cancer. HIF plays a central role in regulating energy metabolism. Currently, the cause of esophageal cancer remains unclear; it may be related to eating coarse food, drinking, smoking, genetics, and esophagitis. Because cancer cells are regulated by multiple survival pathways, research on these regulatory pathways can uncover potential cancer targets. During rapid tumor growth, the insufficient blood supply leads to a hypoxic tumor environment. Many studies have shown that cancer has two major characteristics: HIF-1 expression is upregulated, and metabolic pathways are altered. Even with sufficient oxygen, malignant tumor cells prefer glycolysis to oxidative phosphorylation. This metabolic characteristic of aerobic glycolysis is called the 'Warburg Effect'. Malignant tumor cells exhibit high glucose uptake, active glycolysis, and high lactic acid production. The nearly universal characteristic of primary and metastatic cancers is the upregulation of glycolysis, which results in increased glucose consumption to meet the demands of tumor cells for energy, biosynthesis, and redox signaling. Therefore, in this article, we review recent research on HIF and glucose metabolism in esophageal cancer, which may provide targets for new treatment strategies to improve the therapeutic outcome.

Keywords: Hypoxia, Esophageal cancer, HIF, Glucose metabolism, Warburg effect, Metastasis

Abbreviations: ESCC: esophageal squamous cell carcinoma; RT-qPCR: real-time quantitative polymerase chain reaction; IHC: Immuno histo chemistry; HIF-1α: hypoxia-inducible factor-1 alpha; HIF-2α: hypoxia-inducible factor-2 alpha; GLUT-1: glucose transporter-1; HK-Ⅱ: hexokinase-Ⅱ; LDHA: lactate dehydrogenase-A; Epo: erythropoietin; Epo-R: erythropoietin receptor; VEGF: vascular endothelial growth factor.

Introduction

Esophageal Cancer (EC) is the ninth most common cancer worldwide [1]. Patients with esophageal cancer, whether Esophageal Squamous Cell Carcinoma (ESCC) or Esophageal Adenocarcinoma (EAC), have a relatively high mortality rate [2] that ranks sixth among all cancers, and their five-year survival rate is only 15%–25% [3]. Early detection of esophageal cancer is difficult, and patients are usually diagnosed at an advanced stage [4]. Highly proliferating tumor cells, such as esophageal tumor cells, require a large energy supply [5]. Anaerobic conditions in the tumor can decrease the amount of ATP produced, thus decreasing energy production. Therefore, in order to adapt to this energy shortage, metabolic pathways are modified to let tumor cells upregulate glycolysis. Hypoxia-Inducible Factor (HIF) signaling and metabolic pathway modification can facilitate multiple processes: rapid tumor cell proliferation, neovascularization, invasion and metastasis, and evasion of apoptosis [6]. Traditional treatment options for esophageal cancer include metastatic chemotherapy. However, approximately

half of the patients receiving chemoradiation therapy have local recurrence. In order for radiation therapy to be effective, molecular oxygen is essential. Under normoxic conditions, ionizing radiation generates free radicals and Reactive Oxygen Species (ROS) that damage DNA [7].

Malignant tumor cells are distinct from normal cells of the body because they have the ability to self-proliferate and resist apoptosis. They also have unlimited replication potential, are insensitive to anti-growth signals, and can form a dense vascular network. They can invade, metastasize, and perform aerobic glycolysis. HIF-1 is a core transcription factor that regulates tumor cell adaptation to hypoxia and participates in the transcriptional regulation of many genes during it [8]. Among the major characteristics of tumors, carrying out aerobic glycolysis is critical in giving them great survival advantages.

Basic Structure of HIF

HIF is a heterodimeric protein composed of two subunits, HIF-α and HIF-β, and is the main protein that regulates the response of cells to changes in oxygen levels. The HIF- α family includes: HIF-1α, HIF-2α, and HIF-3α, that are stabilized by oxygen. Under hypoxic conditions, these three isoforms can heterodimerize with HIF-1β to modulate the transcription of target genes [9]. The center of the HIF-1α subunit contains an Oxygen-Dependent Degradation Domain (ODDD); its C-terminus is a transactivation site, which includes two Transactivation Domains (TADs), TAD-N (amino acids 531-575) and TAD-C (amino acids 786-826). The region between the two TAD sequences is an inhibitory domain (ID, amino acids 576-785), which inhibits the transcriptional activation of TAD [10]. Although the regulatory mechanism of HIF-1α synthesis is not dependent on O2, its degradation is. Under normoxic conditions, HIF-1α is rapidly degraded by the intracellular oxygen-dependent ubiquitin protease, and under hypoxic conditions, its expression is induced and maintained [11]. The oxygen-dependent and oxygen-independent regulation of HIF-1α can lead to angiogenesis, metastasis, and cell survival [12,13].

The Role of HIF in Tumors

Hypoxia is an important biological condition that surrounds solid tumor cells. Under hypoxic conditions, gene transcription and expression undergo significant changes in the tumor cells, to adapt to the environment. These genes are the transcriptional targets of HIF-1α. Previous research has found that HIF-1α has more than 70 target genes that are involved in the growth of various types of tumors. The target genes regulated by HIF-1α that promote tumor growth participate in glucose metabolism, cell proliferation, angiogenesis, cell invasion, and other biological behaviors [14].

HIF, Glucose Transport, and Glycolysis

Changes in the energy metabolism of tumors play a prominent role in malignant transformation. Compared to the aerobic oxidation of normal cells, tumor cells under normoxic or hypoxic conditions preferentially use glycolysis to meet metabolic demands [15]. Based on this characteristic, Positron Emission Tomography (PET) technology is used to diagnose malignant tumors in clinical practice. It is widely accepted that HIF-1 is an important mediator in the adaptive response to hypoxia, and is capable of activating and regulating a variety of downstream genes. Among them, genes responsible for regulating energy metabolism include glucose transporters 1 (GLUT1) and 3 (GLUT3), prolyl-4-hydroxylase α1, phosphofructokinase L, lactate dehydrogenase A, aldolases A and C, pyruvate kinase M, enolase 1, hexokinase 1 and 2, and Glyceraldehyde Phosphate Dehydrogenase (GAPDH) [16,17]. Hexokinase is the first enzyme in the glycolysis pathway and irreversibly converts glucose to glucose-6-phosphate, thereby allowing glucose molecules to enter the glycolytic cycle. HIF-1 mainly plays a role in glycolysis [18]. By binding to the target gene, HIF-1 induces the gene expression of glycolytic enzymes, promotes anaerobic metabolism, and facilitates energy production through glycolysis in tumor cells [19]. Thus, current research on the effects of HIF-1 on energy metabolism mainly focuses on tumor cells.

HIF, Tumor Cell Proliferation, and Apoptosis

Studies have shown that an inhibitor of HIF-1α, PX-478, can significantly inhibit proliferation and promote apoptosis of ESCC cells, thus reducing tumor volume and showing significant antitumor activity [20]. On the contrary, HIF-1α-mediated activation of lnc191 transcription promotes the growth and metastasis of ESCC in vitro and in vivo [21]. Another study showed that, in addition to regulating glucose metabolism of tumor cells, HIF-1 can also upregulate multiple growth factors such as erythropoietin, insulin-like growth factor 2, transforming growth factor α, and cyclin D1, allowing liver cancer cells to proliferate, differentiate, and adapt to the hypoxic microenvironment [22].

HIF and Vascularization

The rapid rate of tumor growth leads to a lack of oxygen due to an imbalance between oxygen consumption and insufficient vasculature; thus, tumor hypoxia develops in solid tumors. In many malignant tumors, Vascular Endothelial Growth Factor (VEGF) is one of the main drivers of angiogenesis and is a major factor in the development and maintenance of vascular networks [23]. VEGF increases oxygen supply by directly increasing vascular permeability and inducing the formation of new blood vessels [24]. Studies have shown that there is a positive correlation between HIF-1α and VEGF expression in esophageal tumors, and the expression of HIF-1α and VEGF is significantly upregulated in tumor cells under hypoxia [25]. In an esophageal Three-Dimensional (3D) cell culture system, HIF-1α plays an important role in tumor adaptation and tolerance to the hypoxic microenvironment by directly regulating its target gene VEGF [26].

HIF And Tumor Invasion and Metastasis

Tumor invasion and metastasis are highly dependent on Matrix Metalloproteinases (MMPs) [27]. Under hypoxic conditions, hypoxia-induced upregulation of MMPs greatly enhances the inva-

sive capacity of tumor cells, and causes ECM stiffness and degradation [28]. Shao et al [25] demonstrated that HIF-1α and VEGF play a synergistic role in the invasion and metastasis, and consequent malignancy of esophageal cancer, thus reducing the survival rate of patients with oral squamous cell carcinoma.

HIF And Tumor Resistance to Radiotherapy

Radiation therapy is the standard of care for Esophageal Squamous Cell Carcinoma (ESCC), especially in patients with inoperable tumors in the upper and middle esophagus. Several studies have confirmed that cancer cells may be 2-3 times more sensitive to radiation under normoxic conditions than under hypoxic conditions [29,30]. Many preclinical and clinical studies have shown that tumor cells can be protected from radiotherapy by VEGF [31]. A study of the combination of bortezomib with radiotherapy for esophageal cancer showed that it effectively sensitized ESCC cells to radiation by reducing the expression of HIF-1α and VEGF, activating caspase to induce apoptosis, and delaying DNA damage repair [32]. Similarly, Brucea Javanica Oil Emulsion (BJOE) can inhibit the expression of HIF-1α, alleviate hypoxia, and increase the sensitivity of ESCC to radiotherapy [33].

HIF and the Prognosis of Esophageal Cancer

Esophageal squamous cell carcinoma is a solid tumor, and its internal hypoxia often leads to increased HIF-1α protein expression, which is related to the invasion and metastasis of esophageal cancer [34]. High HIF-1α expression is correlated with poor prognosis in patients with ESCC, suggesting its association with an increased risk of esophageal squamous cell carcinoma. Furthermore, HIF-1α expression is a potential indicator of lymph node metastasis and correlates with tumor stage. HIF-1 is a key transcription factor that transmits hypoxic signals and mediates the effects of hypoxia [35]. HIF-1α regulates both autocrine or paracrine signaling pathways for cell growth to promote angiogenesis in hypoxic conditions [36]. HIF-1α is a functional subunit of HIF-1, it participates in the transcriptional regulation of various target genes and affects the energy metabolism, proliferation, and apoptosis of tumor cells [15,37]. Downstream HIF-1 signaling generates a series of reactions in cells, enabling it to adapt to the hypoxic environment, and promoting tumor vascularization [38]. It also increases tumor invasiveness and resistance to radiotherapy and chemotherapy and participates in tumor progression [39,40]. Unfortunately, the role of HIF-1α in the invasiveness and prognosis of esophageal cancer is still unclear, and research results vary among different cancers, ethnicities, and populations. To date, most clinical studies have relied on immunohistochemical methods and have found that the positive expression rate of HIF-1 is relatively high, between 43.75% and 69.9% [25,41,42]. The positive expression rate is significantly higher in squamous cell carcinoma than in adenocarcinoma [43]. The positive expression rate of HIF-1α is also higher than that of HIF-2α [44]. Increasing research has shown that the positive expression of HIF-1α protein in ESCC is higher in patients at stage T3 or T4 with lymph node metastasis than in patients at stage T1 or T2 without lymph node metastasis [25,45]. Furthermore, HIF-1α protein expression increases with TNM staging [46]. Univariate analysis identified high positive HIF-1α expression as a risk factor for tumor invasion, lymph node and distant metastasis, lymphatic invasion, and positive surgical margins. Cox regression multivariate analysis showed that HIF-1α expression was an independent prognostic factor for 5-year survival. However, opposing results have also been reported [25]. Munipalle et al [43] used immunohistochemistry and found varying levels of HIF-1α expression in 36 patients with ESCC. Furthermore, regression analysis showed that HIF-1α and was HIF-2α not an independent prognostic factor for survival [47,48]. Although the sample size was small, this study indicated that HIF-1α may not have prognostic value in European populations of patients with ESCC. Additionally, in 53 patients with esophageal cancer who received esophagectomy, although HIF-1 mRNA expression was related to protein expression and upregulated to varying degrees in esophageal squamous and adenocarcinoma cells, it was not correlated with histomorphology or prognosis, and the expression did not predict tumor progression, remission, or prognosis [49]. Therefore, the complicated relationships between hypoxia-related molecules HIF-1α, HIF-2α, GLUT-1, RAC-1, and BECLIN-2 and angiogenesis factors VEGF, VEGF-C, VEGF-D, CD34, and E-cadherin in esophageal cancer are still under research [25,42,49-51]. Additional clinical evidence is needed to show clinical utility in the early diagnosis, treatment, and prognosis of esophageal cancer.

HIF Inhibitors and Esophageal Cancer (Treatment)

Semenza and Wang first discovered Hypoxia-Inducible Factor (HIF)-1, established the structure, and determined the coding sequence of its cDNA, which provided the foundation for developing HIF-1 inhibitors against tumors [52]. According to the mechanism of action, HIF inhibitors can be divided into regulators of: HIF-1α mRNA expression, HIF-1α protein translation, HIF-1α protein degradation, HIF-1α DNA binding, and HIF-1α transcriptional activity. PX-478 (S-2-amino-3- [4'-N, N, -bis(chloroethyl)amino] phenyl propionic acid N-oxide dihydrochloride) is a selective inhibitor that inhibits the transcription and translation of HIF-1α. PX-478 inhibits tumor growth in vivo and in vitro, induces cell cycle arrest at the G2 phase, promotes apoptosis, and reduces expression of COX-2 and PD-L1 in ESCC cells [20]. In recent years, the discovery and development of new small molecules targeting HIF-1α have been an exciting direction in the development of therapy, and relevant studies have increased exponentially [12, 53]. However, the main challenge in developing small-molecule HIF-1α inhibitors is their specificity. Hence, further research is needed to explore the potential of HIF-1α inhibitors in esophageal cancer.

Conclusion

Even though living standards have improved, factors such as poor dietary habits and polluted living environments continue to contribute to an increase in the number of patients with esophageal cancer. Esophageal cancer remains a significant cause of cancer-related deaths worldwide. In some Western countries, its incidence

has increased dramatically, with a 5-year survival rate of only 10% to 15% [54]. Most patients are already in an advanced stage at the time of diagnosis and cannot be treated with radical surgical resection. Early-stage esophageal cancer can be removed with surgery. In its middle and advanced stages, where the cancer has already metastasized, resection complemented with neoadjuvant chemotherapy is the main choice of treatment. High-dose chemotherapy drugs can kill cancer cells and reduce tumor volume. Acquired resistance to radiation remains a major obstacle in increasing the survival rate of Esophageal Cancer (EC) [55]. Hypoxia-related factors play a crucial role in resistance to radiation, and 2ME2 inhibits the expression of HIF-1α in ECA-109 cells, sensitizing them to radiation [56]. These findings provide an important foundation for probing into the biological function of HIF as a potential therapeutic target for the treatment of esophageal cancer. Tumor cell metabolism differs from that of normal cells. For example, under hypoxic conditions, HIF-1α can inhibit Pyruvate Dehydrogenase (PDH) by activating Pyruvate Dehydrogenase Kinase (PDK), leading to an accumulation of pyruvate in the cytoplasm [57]. At the same time, the expression of LDH induced by HIF-1α can promote the metabolic cycle of glycolytic cofactor NAD+ by catalyzing the transformation of pyruvate to lactic acid, thereby promoting continuous glycolysis and the production of ATP [15,58-61].

Changes in the glucose metabolism of tumors play a significant role in tumor progression and HIF is one of the key enzymes in glycolysis. The evaluation of hypoxia in esophageal cancer is important for predicting treatment outcomes and efficacy. Many studies have demonstrated that HIF was associated with differentiation and lymph node metastasis, and with the TNM stage, HIF could be a potential independent prognostic factor (Table 1). Novel strategies for the therapeutic targets of HIF in esophageal cancer are to be further explored and may play a role in improving treatment outcomes.

Table 1: Hypoxia inducible factor and Warburg effect in esophageal carcinoma.

Reference	Type of Study	Population, Setting	Method	Factors	Significant findings
de Andrade Barreto et al. [50]	Retrospective, clinical	44 patients of Esophageal Squamous Cell Carcinoma (ESCC)	IHC RT-qPCR	PKM2, GLUT-1, HK-II , HIF-1α	The expression of GLUT-1, HIF-1α, PKM1 and PKM2 were frequently detected in ESCC patients, but not correlated with clinicopathological features.
Zeng et al. [59]	Experimental, in vivo	Esophageal carcinoma cell lines Eca109 and TE13	real-time PCR, Western blot and siRNA interference	HIF-1α, GLUT-1, HK-II ,LDHA	The PI3K/AKT pathway and HIF-1α are both involved in the process of glycolysis in esophageal cancer cells.
Ogane et al. [60]	Retrospective, clinical	96 patients of Squamous Cell Carcinoma (SCCs)	IHC	HIF-1α, GLUT-1, RAC-1	The HIF-1α expression would be an independent indicator for prognosis, GLUT-1 and RAC-1 may be involved in lymph node metastasis.
Griffiths et al. [47]	Retrospective, clinical	177 patients of gastric and gastrooesopageal junction tumours.	IHC	HIF-2α, Epo, Epo-R, GLUT-1, VEGF	Hypoxia-inducible factor-2alpha was expressed in 63% of 177 resection specimens, and has no role as a routine prognostic indicator. The high expression of HIF-2alpha may be of value as a potential therapeutic target.
Shao et al. [61]	Retrospective, clinical	120 patients of curative resection for ESCC	IHC	HIF-1α, p53, VEGF	HIF-1α, p53, VEGF expression not correlated with clinicopathological parameters. Uregulation of HIF-1α is an independent predictor for poor overall survival

Table Abbreviations: ESCC: esophageal squamous cell carcinoma, RT-qPCR: real-time quantitative polymerase chain reaction IHC: Immunohistochemistry, HIF-1α: hypoxia-inducible factor-1 alpha, HIF-2α: hypoxia-inducible factor-2 alpha, GLUT-1: glucose transporter-1, HK-II : hexokinase-II , LDHA: lactate dehydrogenase-A, Epo: erythropoietin, Epo-R: erythropoietin receptor, VEGF: vascular endothelial growth factor.

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Conflict of Interest

The authors declare no conflicts of interest.

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