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# Targeted HIF-1a to Treat Tumors: Mechanisms, Application and Future

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**Abstract:**

Cancer has become one of the major health challenges in the world today. With the growth of population, the change of lifestyle and environmental pollution, the incidence of cancer is on the rise, which presents a major risk to the lives and health of people. At the same time, with the aging of the population and the change of lifestyle, the mortality rate of cancer continues to rise, which brings a heavy burden to society, families and individuals. At present, radiation therapy, chemotherapy, and surgical resection are the three primary cancer treatment methods.HIF-1a as a transcription factor is highly related to tumor proliferation, and related therapeutic strategies have great potential. This article provides an overview of the research on the relationship between HIF-1a and tumors, explains how HIF-1a can be used to stimulate tumor growth and stability, and lists some practical ways to use the HIF-1a transcription factor to treat tumors. It provides a new research direction reference and guidance for the frontier research of tumor therapy, and provides a new possible cure option for tumor patients.

**Keywords:** HIF-1a; tumor therapy; cancer; targeted drug therapy

## 1. Introduction

Malignant tumors, which can cause cancer, have become one of the major health challenges facing the world today. Globally, there were approximately 19.3 million new cases of cancer and 10 million cancer-related deaths in 2020, according to GLOBOCAN 2020.[1]. The harm of malignant tumors to the human body is extremely serious. Its easy diffusion is the biggest obstacle to treatment [2].

Currently, radiation therapy, chemotherapy, and surgical excision are the primary means of treating cancers. [3]. Among them, surgical resection is the most common treatment method which has the possibility of complete treatment but has risk of postoperative complications at the same time; chemotherapy and radiotherapy are using high -energy radiation, drugs to kill tumor cells or inhibit tumor growth, but cause damage to the surrounding healthy tissue simultaneously, or causes sequelae such as hypertension heart disease.

As a result, looking for new tumor treatment is urgent. In modern times, researchers have proposed targeted drug therapy, which is aim at tumor -specific molecules or signal pathways. Targeted medication therapy is more precisely and specifically able to prevent tumor cells from proliferating and from surviving than conventional treatments.[4].

Hypoxia-Inducible Factor 1-Alpha (HIF-1a) is a transcription factor that stabilizes and activates under low oxygen environment [5]. In the tumor environment, the formation of hypoxic environment caused by the rapid growth of tumor tissue promoted the overexpression of HIF-1a. Besides, the overexpression of HIF-1a was further linked to the growth of tumor tissue. Thus, a potential treatment method for inhibiting the growth and progress of tumor through targeted therapy to inhibit the expression or function of HIF-1a [6].

The application of HIF-1a in tumor treatment is still in the research stage, but some encouraging progresses have been achieved. It is necessary to further research and clinical experiments to improve this treatment strategy. In this article, the author summarizes the literatures concerning the interaction between HIF-1a and tumor cells, intending to serve as a resource for the emerging field of tumor treatment research.

## 2. How to Use HIF-1a to Treat Tumors

### 2.1 The Role of HIF-1a in the Spread of Tumors

HIF-1a is crucial for the growth of tumors. It is mainly involved in the following aspects of tumor proliferation:

(1) Promoting angiogenesis: HIF-1a has been shown to

stimulate tumor angiogenesis, these blood vessels can transport oxygen and nutrients for tumors, which is necessary for tumor growth. To create new blood vessels and supply oxygen and nutrients to tumors, HIF-1a stimulates the transcription of several related genes, including vascular endothelial growth factor (VEGF), when the body is hypoxic [7].

(2) Energy metabolism regulation: Research has shown that HIF-1a can control tumor cells' energy metabolism and increase their ability to adapt to a hypoxic environment. HIF-1a causes a metabolic shift from oxidative phosphorylation to glycolysis and lactate production under hypoxic conditions, which in turn preserves the energy supply and survival of tumor cells. This excess pyruvate, alanine, and lactate production is caused [8].

(3) Cell cycle regulation: Research has revealed that HIF-1a plays a role in controlling tumor cells' cell cycle and encouraging their growth and multiplication. HIF-1a can promote the cell cycle by regulating the expression of cell cyclin-related proteins, and then promote the proliferation of tumor cells [9].

(4) Cell apoptosis inhibition: It has been discovered that HIF-1a can prevent tumor cells from dying by triggering and controlling the expression of several genes linked to apoptosis, hence enhancing the survival and growth of tumor cells [9].

(5) Enhancing stem cell characteristics: It has been discovered that the preservation of cancer stem cell characteristics is intimately correlated with HIF-1a activity. HIF-1a has the ability to control the expression of several genes linked to stem cells, preserving the stem cell properties of tumor cells and encouraging tumor growth and recurrence [10].

In summary, HIF-1a contributes to tumor proliferation through a variety of pathways. Therefore, the intervention of HIF-1a is one of the effective ideas for cancer treatment.

### 2.2 How to Inhibit HIF-1a to Inhibit Tumor Proliferation

Understanding how HIF-1a is involved in tumor proliferation, the next question is how to inhibit HIF-1a to inhibit tumor proliferation.

(1) HIF-1a-targeting small molecule inhibitors: A number of small molecule drugs, including YC-1 [11] and PX-478 [12], have been shown to block HIF-1a's activity. By blocking HIF-1a's activity and stability, respectively, these medicines prevent tumor growth and angiogenesis. By decreasing the stability and transcriptional activity of HIF-1a, KC7F2 prevents the growth of tumors and the formation of new blood vessels [13]. At present, many studies are under way to develop and optimize these small molecule inhibitors to improve their efficacy in tumor therapy.

(2) Oxygen therapy: HIF-1a is easily degraded by protease in an environment with normal oxygen concentrations because its stability is affected by oxygen levels. It is also unable to bind to Hif1α to form dimers or to specific DNA sequences to stimulate the transcription of target genes. On the other hand, high oxygen pressure can be applied to the tumor tissue in order to restore a normal oxygen concentration environment. This can lessen the amount of hypoxia present in the tumor tissue, which will decrease HIF-1α stability and activity [14].

(3) RNA interference: RNAi technology can silence the expression of HIF-1α gene by introducing specific siRNA or shRNA to inhibit its activity. Through RNAi technology, the level of HIF-1α can be effectively reduced, and then its promoting effect on tumor proliferation can be reduced [15].

(4) Antibody therapy targeting HIF-1α: Specific antibodies can specifically bind to HIF-1α and prevent it from binding to its DNA, thereby inhibiting its transcriptional activity and reducing the promotion of tumor proliferation. One monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) is bevacizumab, which can also indirectly alter HIF1α activity by inhibiting tumor angiogenesis [16]. PX-12, an antibody that targets HIF-1α, prevents angiogenesis and tumor growth by preventing HIF-1α from functioning [17].

## 3. Advantages and Disadvantages of Using HIF-1a to Treat Tumors

### 3.1 Advantages

At present, the method of using HIF-1a to treat tumors is mainly targeted drug therapy, so it has most of the advantages of targeted drug therapy:

(1) High efficiency and accuracy: HIF-1a targeted medications have the ability to precisely target the particular signaling molecules and signaling pathways connected to HIF-1a proliferation in tumor cells. This has the benefit of being both highly efficient and accurately targeted. Echinomycin, a substance that targets HIF-1a, was found to be highly targeted and effective in inhibiting the growth, metastasis, and angiogenesis of triple-negative breast cancer [18].

(2) Small side effects: compared with traditional chemotherapy and radiotherapy, HIF-1a-targeted drugs only target tumor cells, reducing the damage to normal cells around the tumor tissue, with fewer side effects. In vitro and in vivo tests of esophageal squamous cell carcinoma were conducted by the researchers, who also evaluated the toxicity to normal cells and reduced tumor growth.

The findings demonstrated that PX-478 could significantly suppress the proliferation of ESCC cells while having minimal impact on normal cells [19].
(3) Designability: Referring to the research of targeted drug therapy, such as the targeted therapy of esophageal squamous cell carcinoma, many targeted drugs against different molecular targets have been designed and applied in clinical practice [20]. For different tumor cells, with the progress of science and technology, it is feasible to design different HIF-1a targeted drugs to target tumors with different molecular characteristics, so as to achieve personalization and improve pertinency.
(4) Combined treatment strategy: HIF-1a-targeted drugs can be combined with other therapeutic methods such as radiotherapy, chemotherapy, immunotherapy, etc., to form a combined treatment strategy to further improve the therapeutic effect. Researchers have improved the efficacy of endostatin endostar combined with cytotoxic chemotherapy [21].

### 3.2 Disadvantages

The use of HIF-1a for cancer therapy also has certain disadvantages. Some of the problems identified with targeted therapy also occur with HIF-1a-targeted therapy: 1. Drug resistance: Tumor cells can bypass inhibition through diverse pathways, such as changes in cell signaling pathways, gene mutations, and other mechanisms. In HIF-1a-targeted drug therapy, tumor cells may be able to evade the effects of HIF-1a inhibition through the compensatory activity of HIF-2a. 2. Heterogeneity: There are different gene expression and metabolic pathways between different tumor types, which may lead to different roles of HIF-1A in different tumors, so the treatment strategy requires different personalized adjustment, increasing the cost.
At the same time, HIF-1a is an important transcription factor involved in regulating the expression of a variety of genes. Inhibition of HIF-1a may have adverse effects on the physiological processes of normal cells, leading to side effects. Due to the lack of clinical trials, the safety and efficacy of this aspect have not been guaranteed.

## 4. Future Perspectives for HIF-1a Tumor Therapy

The development prospect of HIF-1a tumor therapy is very broad. Here are some prospects and ideas for this technology.
(1) To the clinical application stage: In recent years, HIF-1a tumor therapy has entered the clinical trial stage. With more trials and investment, it is expected to gradually move to the clinical application stage, bringing more cure options for cancer patients.
(2) Development of new drugs: through a large number of trials and tests, more kinds of HIF-1a targeted drugs have been developed, such as small molecule inhibitors, antibody drugs, nucleic acid inhibition drugs, etc. Improve the specificity of drugs, optimize the treatment plan and reduce its side effects.
(3) Overcoming drug resistance: through the in-depth understanding of the mechanism of drug resistance in tumor tissue, we can find a way to overcome the drug resistance in tumor tissue from the mechanism. Such as the development of new targets.
(4) Improving efficiency and accuracy: with the continuous progress of technology, new drugs are developed and drug resistance is overcome. It is possible to regulate HIF-1a activity with greater precision. For example, through gene editing and other technologies, the expression level of HIF-1a can be adjusted at a specific time or location, so as to achieve more precise treatment.
(5) Personalized treatment and combination strategy: With the deepening understanding of tumor mechanism, we can better develop targeted treatment strategies according to the characteristics of different tumors and their subtypes, and can combine chemotherapy, radiotherapy, and other targeted therapy methods to maximize the therapeutic effect.

## 5. Conclusion

Malignant tumor is one of the major health challenges in the world today. It has a variety of negative effects on the overall health of the body, such as inhibiting the function of the immune system, causing weight loss, causing pain, and so on. Currently, radiation, chemotherapy, and surgical resection are the main cancer treatment modalities. These therapies do, however, have a number of dangers and adverse consequences. Thus, the development of novel cancer therapies is essential.
One transcription factor that plays a major role in tumor growth is HIF-1a. This review extends and summarizes several appropriate HIF-1a tumor therapies by understanding the role of HIF-1α in tumor proliferation and analyzes the literature on the relationship between HIF-1a and tumor cells: Tumor treatment outcomes can be attained by blocking HIF-1a activity and stability by the use of small molecule inhibitors, oxygen therapy, RNA interference, and certain antibodies. The use of HIF-1a in tumor treatment has several benefits, including high efficacy, little side effects, designability, and the ability to be used in conjunction with other therapeutic approaches.
However, there are also some disadvantages, such as drug resistance and tumor heterogeneity. What can be demonstrated is that HIF-1a therapy has potential in tumor thera-

py, but further research and improvement are needed.
In the future, HIF-1a therapy will be pushed into clinical trials, providing new options and higher cure expectations for cancer patients.

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