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Hypoxia in Cancer: Significance and Impact on Cancer Therapy

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Role of Hypoxia in Cancer Therapy: Introduction

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Abstract

Hypoxia and the hypoxia-inducible factors (HIFs) regulate various characteristic features of cancers such as genetic instability, dedifferentiation, metabolic alterations, neovascularization, metastasis, and drug resistance. Therefore, targeting the hypoxic phenotype is a good approach to eradicate malignant cells. Theoretically, HIF inhibition could overcome the resistance to chemotherapy. So, HIF inhibitors are useful targets in the treatment of cancer. Researchers are trying to get specific HIF-1 inhibitors for successful clinical exploitation. HIFs mediate the response, primarily by acting as transcription factors, which are also good targets for treatment.

Keywords

Hypoxia · HIFs · Metastasis · Malignant cells · Cancer therapy

11.1 Introduction

As the malignant cells proliferate uncontrollably, the cells far away (more than 200 m) from the blood vessels are affected by hypoxia. Invasive oxygen electrodes provide a direct measurement of oxygen tension in the tumor tissue. Although hypoxia is not clearly defined, about 8–10 mm Hg (~1%) is taken as the critical

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pO_2 (Hockel and Vaupel 2001). Hypoxia in the cancer tissue is an independent prognostic factor for cancer mortality. Hypoxia will select tumor cells to more resistant phenotypes (Roma-Rodrigues et al. 2019). Two recent reviews will give more light on this subject (Jing et al. 2019a; Nejad et al. 2021).

11.2 Hypoxia-Inducible Factor

Hypoxia-inducible factor (HIF) regulates the genes involved in the progression of cancer cells. HIF expression is associated with poor prognoses (Huang et al. 2017). HIF is a transcription factor, composed of two subunits, alpha and beta. The alpha unit is oxygen-sensitive, while the beta subunit is constitutive in nature (Semenza 2003). In mammals, there are three alpha isoforms (HIF-1α, HIF-2α, and HIF-3α). HIF-1 and HIF-2 have unique target specificities. HIF-1 induces the expression of glycolytic genes, while HIF-2 targets other genes (Wigerup and Påhlman 2016). The HIF-1α is overexpressed in various cancers, including breast, colon, gastric, lung, skin, prostate, and renal carcinomas compared to their normal tissues (Simiantonaki et al. 2008). HIF also contributes to chemotherapy resistance.

11.3 Tumor Angiogenesis

The upregulation of angiogenesis is a characteristic feature of hypoxia. Cells grown under hypoxic conditions activate transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGF-β), and angiopoietin-2, all of them leading to endothelial cell proliferation (Kelly et al. 2003).

Monoclonal antibodies that target VEGF (bevacizumab) or small-molecule inhibitors that target VEGF receptors have achieved clinical benefits for advanced cancer.

11.4 Metabolic Derangement

In 1924, Otto Warburg observed that many types of cancer cells prefer glycolysis rather than oxidative phosphorylation. Glycolysis generates only two ATP molecules per glucose molecule compared to 32 ATP molecules per glucose molecule during the TCA cycle. Under oxygen-deprived conditions, normal cells also convert pyruvate into lactate, a process known as "anaerobic glycolysis." However, cancer cells convert pyruvate into lactate even when oxygen is available, so their metabolism is often referred to as "aerobic glycolysis" or "the Warburg effect." In that sense, cancer cells prefer a pathway that produces less ATP. One explanation is that cancer cells do have enough nutrient supply, so they do not require maximal ATP production. Another reason is that the HIF-1 directly targets the gene encoding pyruvate dehydrogenase kinase 1 (*PDK1*). The increase in glycolysis for ATP

generation in cancer cells is frequently associated with resistance to doxorubicin and ara-c (Kim et al. 2006).

11.5 Tumor Immune Response

Hypoxia leads to immunosuppression and tumor resistance (Palazon et al. 2012). Tumor hypoxia and HIFs can attract suppressor cells and tumor-associated macrophages with immunosuppressive functions. Hypoxia also suppresses infiltrating cytotoxic T-lymphocyte activity in a HIF-1α-dependent manner.

11.6 Tumor Metastasis

Hypoxia and HIFs are involved in many different steps of the metastatic process. Epithelial-to-mesenchymal transition (EMT) is an initial step in which tumor cells lose expression of the intercellular adhesion molecule E-cadherin (encoded by *CDH1*) and acquire a motile phenotype. Hypoxia and HIFs can also induce tumor cell invasion through various mechanisms including upregulation of cathepsin D, urokinase-type plasminogen activator receptor, and matrix metalloproteinases. Activation of HIF-1 and -2 is associated with loss of E-cadherin, so as to increase invasion and metastasis. The HIF also upregulated proteins implicated in matrix remodeling, such as lysyl oxidase (LOX) and metalloproteases. In addition, HIF activates genes involved in metastasis and invasion, such as the *c-met* proto-oncogene and the chemokine receptor CXCR4 (Chan and Giaccia 2007).

11.7 Chemoresistance

In the majority of patients, the cause for treatment failure is the resistance to cancer therapy. Hypoxia induces drug resistance in a wide range of neoplastic cells, including mouse embryonic fibroblasts. When HIF-1 is inactivated, the effect of carboplatin and etoposide on cell proliferation is significantly enhanced. HIF-1α can be used as a marker of the survival rate of cancers. Hypoxia is a crucial mediator of chemoresistance. HIF overexpression in clinical samples is associated with therapeutic resistance or decreased survival following IR or chemotherapy (Lin and Koong 2018).

11.8 Hypoxia and Drug Resistance

In response to hypoxia, the HIF-1 activates the multidrug resistance 1 (*MDR1*) gene. The MDR1 gene encodes the drug efflux pump, P-gp, which decreases the intracellular concentration of various chemotherapeutic drugs (Tameemi et al. 2019).

11.9 Hypoxia and New Treatment Modalities

Hypoxia is very characteristic of solid tumors, and hypoxia mediates metastasis and resistance to chemotherapy. Therefore, hypoxia is the most attractive therapeutic target. Hypoxia-activated prodrugs, specific targeting of HIFs, or targeting pathways important in hypoxic cells such as the mTOR and UPR pathways have been tried (Semenza 2012).

11.10 Hypoxia-Activated Prodrugs

Prodrugs are activated in hypoxic tissue and then selectively kill hypoxic tumor cells have been tried. For example, tirapazamine has been extensively tested in clinical trials, but results are disappointing (DiSilvestro et al. 2014). The prodrug apaziquone (EO9), a mitomycin C derivative, showed efficacy in preclinical studies, but clinical trials were negative. The phase II clinical trial on the TH-302 combined with gemcitabine for pancreatic cancer is encouraging.

11.11 Drugs Targeting Hypoxic Signaling

Targeting HIF directly and targeting of downstream HIF signaling pathways have also been tried. Thus, monoclonal antibodies targeting VEGF (bevacizumab) or small-molecule inhibitors targeting the VEGF receptor have shown clinical benefits in advanced cancers. Translation of HIF-α mRNA is controlled by the PI3K/AKT/mTOR pathway. Thus, mTOR inhibition decreases HIF-1α and HIF-2α levels under hypoxic conditions (Mohlin 2015).

11.12 Topoisomerase 1 Inhibitors

Irinotecan and topotecan are topoisomerase-I inhibitors. Topotecan inhibits HIF-1α translation (Bertozzi et al. 2014). EZN-2968 is a synthetic antisense oligonucleotide, complementary to the mRNA coding sequence of human HIF-1α. The EZN-2968 binding leads to HIF-1α mRNA downregulation in a dose-dependent manner (Jing et al. 2019b).

11.13 Heat Shock Protein Inhibitors

Heat shock proteins (Hsp) are cellular chaperones. Hsp90 inhibitor geldanamycin (GA) can induce proteasomal degradation of HIF-1α under hypoxic conditions. The GA analogs 17-AAG (tanespimycin) and 17-DMAG (alvespimycin) and EC154 have been evaluated in phase I and phase II trials. Alteration in protein ubiquitylation

is commonly associated with cancer. Ubiquitylation can be opposed by deubiquitinases (DUBs), which have emerged as promising drug targets. There is a reciprocal regulation of DUBs by hypoxia, and therefore DUB-specific drugs may be useful in cancer therapy (Mennerich et al. 2019).

11.14 Inhibitors of HIF Transcriptional Activity

The HIF transcription is dependent on co-activators such as p300/CBP. Therefore, transcriptional inhibition has been tried as a therapeutic intervention. *Chetomin*, a fungus metabolite, could inhibit binding of HIF to p300, and in vivo anti-tumor effects were also demonstrated.

11.15 Proteasome Inhibitors

The proteasome inhibitor bortezomib blocked hypoxia-induced VEGF accumulation by inhibiting HIF-1α transcriptional activity. However, in a phase II trial, bortezomib was inactive in patients with metastatic colorectal cancer (Marignol et al. 2013).

Such targeted strategies include hypoxia-activated prodrugs, inhibition of HIF dimerization, decreasing transcriptional activity, siRNA treatment, as well as suppressing the PI3K/AKT pathway (Zhang et al. 2021). A combination of immunotherapy and HIF inhibition could be a better therapeutic approach.

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