*Editorial*

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# Hypoxia-Inducible Factors: Novel Molecular Target Remains to be Explored as Anticancer Agent in Advanced Human Cancers

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**Abstract**

Hypoxia-inducible factors (HIFs) are transcription factors that are expressed as cellular adaptations in order to improve the metabolism as well as neovascularisation in the hypoxic tumor microenvironment. HIFs induce the expression of various genes of proteins such as vascular endothelial growth factors and platelet-derived growth factors that have a central pivotal role in the angiogenesis and inflammation. Accounting the role played by HIFs, many recent studies highlighted the significance of therapeutic potential of HIF-targeted antagonists. Agents that block the nuclear localization of HIF-1alpha or that which inhibits the dimerization of HIF-1, or the one that inhibits the HIF-1alpha/HIF-2alpha mediated induction of VEGF were demonstrated as effective antiangiogenic agents in advanced cancers. This short communication describes a recent highlight on the need of targeting the HIFs.

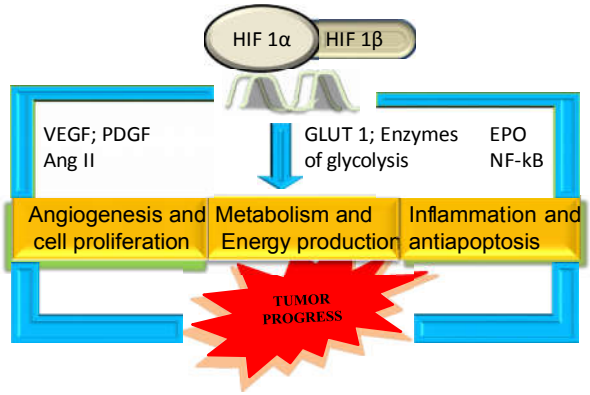
**Keywords**: Hypoxia-Inducible Factor; Antagonists; Clear Cell Renal Cell Carcinoma; Angiogenesis; Hypoxia; Normoxia.

Low oxygen tension has long been described in the tumor microenvironment [1]. Among the various adaptations of tumor such as angiogenesis and anaerobic glycolysis which have a significant role to survive such hypoxic microenvironment. Such adaptations favor for the advancement, progression and metastasis of tumor. Hypoxia- inducible factors (HIF) are transcription factors that are synthesized during the low oxygen tension of < 5% through several molecular signalling pathways. Among the two subunits of HIF, HIF-alpha is the inducible form present in the cytosol while the constitutively expressed beta remains in the nucleus. For HIF-alpha, various isoforms-HIF-1alpha, 2- alpha and 3- alpha- were described [2,3].

The active heterodimeric form of the subunits HIF-1/2 alpha with HIF-beta is formed inside the nucleus, binding to the response element and finally alters the expression of targeted genes whose products are involved in the metabolic adaptation of tumor cells. The HIF alpha subunits are regulated by phosphorylation followed by ubiquitinylation and proteasomal degradation under normal oxygen tension which is favored by tumor suppressor proteins, p53 and von Hippel-Lindau (VHL) [4,5]. Therefore, mutational inactivation of these proteins prevents the degradation and thereby, consistently maintains the HIF-alpha level in the cytosol. Among the various factors that increase the expression of HIF-alpha, the role of mitochondria-derived reactive oxygen species (ROS) mainly during the impaired oxidative phosphorylation under hypoxic condition were demonstrated as well [4]. Though HIFs have no effect on the transcription of enzymes of Krebs cycle or beta-oxidation, they express all the key glycolytic enzymes in order to favour an anaerobic glucose oxidation. Furthermore, fatty acid synthesis can also be promoted by HIFs. Vascular endothelial growth factor (VEGF) and erythropoietin are the two major proteins expressed to favor angiogenesis and inflammation, respectively. Nuclear factor kappa B acts as a direct modulator, in addition to the growth factors, chemokines, cytokines and ROS- generated during the inflammation- can turn up the expression of HIF-alpha. This signifies the role of inflammatory process in the tumor microenvironment as a promoter of HIF-alpha expression and advancement of tumor.

Activation of HIFs was demonstrated to be involved directly in many human cancers. Both HIF-1 and 2-alpha were highly expressed in the invasive breast cancer specimen [6]. Similarly, in neuroblastoma and gallbladder adenocarcinomas angiogenesis was

induced by both HIF-1 alpha and HIF-2 alpha [7,8]. Human sporadic clear cell renal cell carcinoma (RCC) samples showed higher expression HIF-2 alpha than HIF 1alpha where loss of VHL was found [9,10]. Novel multi-targeted receptor kinase inhibitors including VEGFR tyrosine kinase inhibitors (sunitinib, imatinib, cabozantinib and everolimus) were described to be the first-line therapy especially for the advanced RCC [11,12]. However, most of the antiangiogenic agents that act against the VEGF receptor showed not only moderate survival benefit but adverse effect such as hypertension, leucopenia and risk for thrombotic events. Accounting the role of HIF-alpha recent studies highlighted the significance of therapeutic potential of HIF-alpha targeted antagonists. However, only few agents were experimentally evaluated. Topotecan, a topoisomerase I can inhibit the HIF-1alpha and HIF-2alpha mediated induction of VEGF during hypoxia in neuroblastoma cells [13]. Another agent Acriflavine was effective to inhibit the dimerization of HIF-1 in mice bearing prostate cancer xenografts and thereby, prevent the tumor growth and neovascularization [14]. These results revealed that small molecules can inhibit dimerization of HIF-1 and hence have potent inhibitory effects on tumor growth and vascularization. Recent studies reported Benzophenone-1B can block the nuclear localization of HIF-1alpha and thereby impairs the angiogenesis [15]. More experimental and clinical trials in the near future will explore many HIF antagonists for the treatment of progressive or recurrent cancer cases.




Cellular adaptation mechanism of hypoxia-inducible factors (HIFs) during hypoxia. VEGF: Vascular endothelial growth factor; PDGF: Platelet derived growth factor; EPO: Erythropoietin; GLUT-1: Glucose transporter-1; Ang-2: Angiopoietin-2; NF-kB: Nuclear factor- kappa B.

## References

1. Padhani AR, Krohn KA, Lewis JS, Alber M. Imaging oxygenation of human tumours. Eur Radiol. 2007; 17:861-72.
2. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol (1985). 2000; 88:1474-80.
3. Suzuki N, Gradin K, Poellinger L, Yamamoto M. Regulation of hypoxia-inducible gene expression after HIF activation. Exp Cell Res. 2017 [Epub ahead of print].
4. Chowdhury AR, Long A, Fuchs SY, Rustgi A, Avadhani NG. Mitochondrial stress-induced p53 attenuates HIF-1á activity by physical association and enhanced ubiquitination. Oncogene. 2017; 36:397-409.
5 Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999; 399: 271-5.
6. Helczynska K, Larsson AM, Holmquist Mengelbier L, Bridges E, Fredlund E, Borgquist S, Landberg G, Påhlman S, Jirström K. Hypoxia-inducible factor-2alpha correlates to distant recurrence and poor outcome in invasive breast cancer. Cancer Res. 2008; 68:9212-20.
7. Puppo M, Battaglia F, Ottaviano C, Delfino S, Ribatti D, Varesio L, Bosco MC. Topotecan inhibits vascular endothelial growth factor production and angiogenic activity induced by hypoxia in human neuroblastoma by targeting hypoxia-inducible factor-1alpha and -2alpha. Mol Cancer Ther. 2008; 7:1974-84.
8. Giatromanolaki A, Sivridis E, Simopoulos C, Polychronidis A, Gatter KC, Harris AL, Koukourakis MI. Hypoxia inducible factors 1alpha and 2alpha are associated with VEGF expression and angiogenesis in gallbladder carcinomas. J Surg Oncol. 2006; 94: 242-7.
9. Yin Q, Hung SC, Wang L, Lin W, Fielding JR, Rathmell WK, Khandani AH, Woods ME, Milowsky MI, Brooks SA, Wallen EM, Shen D. Associations between Tumor Vascularity, Vascular Endothelial Growth Factor Expression and PET/MRI Radiomic Signatures in Primary Clear-Cell-Renal-Cell-Carcinoma: Proof-of-Concept Study. Sci Rep. 2017; 7:43356.
10. Martínez-Sáez O, Gajate Borau P, Alonso-Gordoa T, Molina-Cerrillo J, Grande E. Targeting HIF-2 alpha in clear cell renal cell carcinoma: A promising therapeutic strategy. Crit Rev Oncol Hematol. 2017; 111:117-123.
11. US Food and Drug Administration approves new treatment for gastrointestinal and kidney cancer (2006). https://www.fda.gov/NewsEvents/Newsroom/Press Announcements/ 2006/ ucm108583.htm.
12. Tannir NM, Schwab G, Grünwald V. Cabozantinib: an active novel multikinase inhibitor in renal cell carcinoma. Curr Oncol Rep. 2017; 19:14.

13. Puppo M, Battaglia F, Ottaviano C, Delfino S, Ribatti D, Varesio L, Bosco MC. Topotecan inhibits vascular endothelial growth factor production and angiogenic activity induced by hypoxia in human neuroblastoma by targeting hypoxia-inducible factor-1alpha and -2alpha. Mol Cancer Ther. 2008; 7:1974-84.

14. Lee K, Zhang H, Qian DZ, Rey S, Liu JO, Semenza GL. Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. Proc Natl Acad Sci USA. 2009; 106:17910-5.

15. Thirusangu P, Vigneshwaran V, Ranganatha VL, Vijay Avin BR, Khanum SA, Mahmood R, Jayashree K, Prabhakar BT. A tumoural angiogenic gateway blocker, Benzophenone-1B represses the HIF-1 alpha nuclear translocation and its target gene activation against neoplastic progression. Biochem Pharmacol. 2017; 125:26-40.