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TARGETING HIF-1 PATHWAY: A THERAPEUTIC APPROACH TO KILL CANCER CELLS

Ajaz Ahmad Waza[1*], Shabir Ahmad Bhat[1], Zeenat Hamid[2]

[1]Centre of research for development (CORD) University of Kashmir, Srinagar, Jammu and Kashmir, 190006, India. ajazahmad09@gmail.com, bhatshabir2007@gmail.com
[2]Department of Biotechnology, University of Kashmir, Srinagar, Jammu and Kashmir, (190006) India. zeenathmd269@gmail.com

Abstract:
Tumorous growth often faces hypoxic (low oxygen tension) conditions and the adaptations of these cells to hypoxic conditions determine their survival. The cancer cells respond to hypoxia by altering the expression of different genes and Hypoxia-Inducible Factor (HIF)-1 is one of it. HIF-1 is a transcriptional factor that response to hypoxia (low oxygen tension) conditions quickly. Expression of HIF-1 gene is essential for increase in vascularization of hypoxic region such as tumor and thus aid in proliferation and survival of cancerous cells. Moreover, HIF-1 signaling in cancer cells has a diverse influence on the metastatic cascade. Targeting HIF-1 is therefore one of the most promising approach to treat cancer. In this review, we have focused on the potential of targeting HIF-1 pathway as therapeutic intervention to treat cancer.

Key words: HIF-1 Pathway, Cancer, *Hypoxia-Inducible*

***Corresponding author:**
Ajaz Ahmad Waza,
Centre of research for development (CORD),
University of Kashmir, Srinagar, Jammu and Kashmir,
190006, India.
E-Mail:ajazahmad09@gmail.com, bhatshabir2007@gmail.com

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INTRODUCTION:

Hypoxia is the deficiency either in the delivery or the utilization of oxygen at the cellular level, which can alter various physiological functions of the cells, with severe consequences to the organism. In humans, the hypoxic conditions occur during various pathophysiological conditions, like tumorous growth, myocardial ischemia, stroke etc [1] [2] [3]. When cells sense a decrease hypoxia, they develop adaptive responses in order to sustain this condition and survive. If hypoxia lasts too long or is too severe, the cells eventually die [4]. Interestingly, tumorous growths often face hypoxic conditions and the adaptations of these cells to hypoxic conditions determine the prognostic potential of the tumors. Indeed, it has also been shown that hypoxia contributes to the selection of cells with decreased apoptotic potential and high metastatic capability [5]. The cells respond to hypoxia by altering the expression of various genes and most important one is HIF-1 [6].

One of the important signaling pathways activated during hypoxia conditions in cancer cells is HIF-1 signaling. HIF-1 is a heterodimeric consists of α-subunit (oxygen-regulated) and β-subunit (constitutively expressed). The HIF-1α subunit is oxygen sensitive due to the presence of an oxygen-dependent degradation (ODD) domain. Under normal conditions, prolyl hydroxylases hydroxylate HIF-1 α subunit at proline residues and triggers their proteasomal degradation [7] [8] [9] [10]. But under hypoxia conditions, HIF-α is stabilizes and translocated to nucleus, as prolyl hydroxylases are inhibited. Within nucleus HIF-α dimerize and bind to hypoxia-responsive elements (HREs) of allow their expression. It should be noted here that HIF-1 allows expression of 100s of genes and thus boost cellular capacity to survive in hypoxia environment (see figure 1). The microenvironment around the tumorous area is highly hypoxic, but activation of HIF-1 allows proliferation of such tumors by enhancing angiogenesis. Increased angiogenesis increases oxygen supply to the cancerous area and therefore promote their growth [11] [12]. So based on its central role in survival of cancer cells, manipulation of HIF-1 activity in tumor masses has emerged as a focus now-a-days to develop pharmaceutical and noninvasive treatment, as an alternate options for cancer patients.

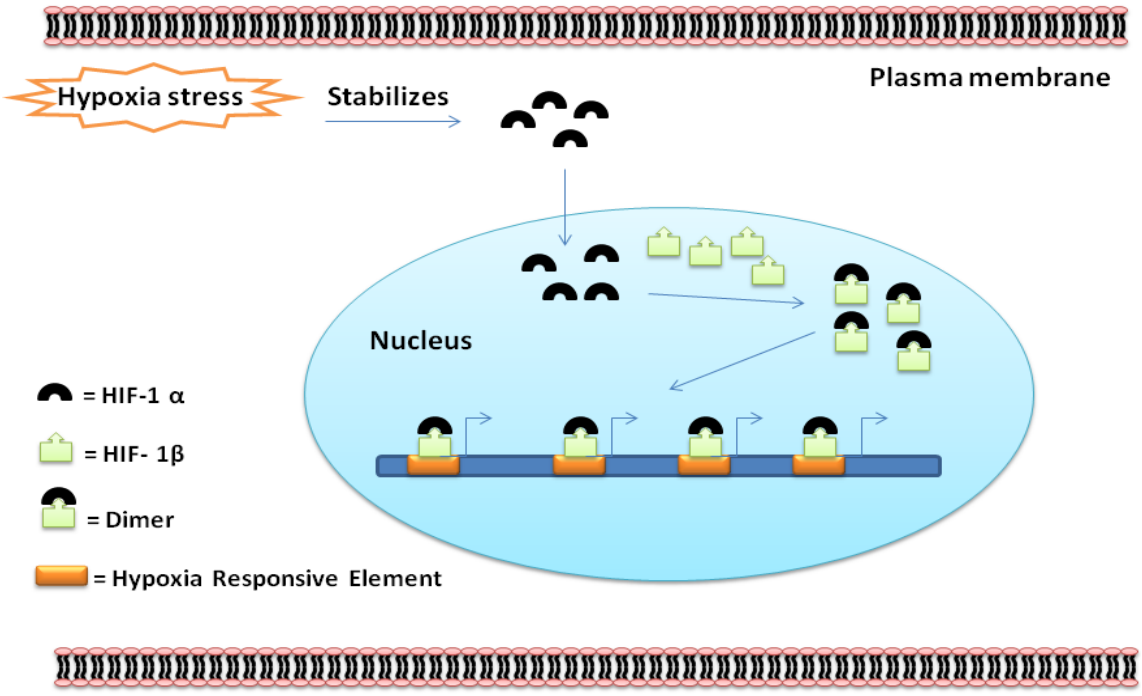

Fig. 1: Shows activation of HIF-1 pathway: During hypoxia stress, HIF1-α gets stabilize and is tranlocated to nucleus, where it dimerizes with HIF1-ß to form a complex. The dimer recognizes the HREs on the target genes and allows their expression.

Table 1: Human cancers exhibiting increased levels of HIF-1 protein.

Cancer type	References
Bladder cancer	**[13]**
Breast	[14]
Cervical cancer	[15]
Colon cancer	[16]
Colorectal cancer	[17]
Endometrial cancer	[18]
Esophageal Squamous cell carcinoma (SCC)	[19]
Gastrointestinal stromal tumor	[20]
Glioma	[21]
Head and neck SCC	[22]
Laryngeal cancer	[23]
Liver cancer	[24]
Lung cancer	[25]
Melanoma	[26]
Oligodendroglioma	[27]
Ovarian cancer	[28]
Prostate cancer	[29]
Renal cancer	[30]

Proper oxygen (O_2) supply is required by the mammalian cells to grow, proliferate and to maintain aerobic metabolism properly. However in tumor cells O_2 supply is impaired due to decrease in O_2 delivery and diffusion and therefore hypoxic condition is created. Hypoxia is considered as a prominent characteristic feature in the tumor tissue which drives aggressiveness of a tumor mass [31]. It should be noted here that the cancer cells counter this hypoxia conditions by activating HIF-1 pathway, which inturn modify the cellular environment to combat the hypoxic stress condition. HIF-1 plays a central role in hypoxia and is therefore considered to be an essential protein in tumor proliferation [32]. The expression level of HIF-1 is increased in different tumor tissues and positively correlates with tumor aggressiveness and poor prognosis (see table 1). To further support the role of HIF -1 in cancer progression, it has been found that loss of HIF-1α function is associated with the decrease in tumor growth, vascularization, and metastasis.

As earlier stated, HIF-1 activation is responsible for the tumor progression, and therefore inhibiting its activation could be used as a therapeutic approach in cancer. However, the HIF-1 pathway is a highly complex mechanism and involves activation of a diverse proteins, each of which may serve target to in an anti cancer therapy approach [33]. Down regulation of HIF-1 protein is considered to be the main strategy that could be attained via activation of hydroxylases. Actually such hydroxylases belong to the 2-oxoglutarate (2OG)-dependent oxygenase superfamily and require a ferrous ion, as a cofactor for activation. Treatment of cells with iron and ascorbate has been found to decline HIF-1 protein levels and its target genes [34]. Till date, many types of HIF-1 inhibitors have been discovered and some are under clinical trials. Each inhibitor act via a specific mode of action to manipulate HIF-1 pathway and some of the inhibitors are mentioned here. Echinomycin, nutlin-3 and bortezomib inhibit the HIF-1-mediated gene expressions [35] [36] [37]. Microtubule disruptors, HSP90 inhibitors, and YC-1 destabilize HIF-1α in the post-translational level [38] [39] [40]. Some other agents such as topotecan, digoxin, PX-478, rapamycin and chaetocin block de novo synthesis of HIF-1α protein [41] [42] [43] [44] [45]. Similarly HIF-1α inhibition by using siRNA *in vivo* and *in vitro* has been reported to decreased growth and metastasis of cancerous cells [46] [47] [48]. More and more understanding of the HIF-1 domains like their structure and molecular biology will result in unearthing therapeutic molecules.

CONCLUSION:

Hypoxia is a well known phenomenon in solid tumor masses due to insufficient vascularization. Cancer cells activate HIF-1 pathway to deal with this O_2 stress, which inturn support a vast number of cellular processes. As HIF-1 protein has a well known role in supporting growth and proliferation of cancerous cells and therefore its targeting has emerged an alternate way to deal with the tumor growth. It should be noted here that till date no specific HIF-1α inhibitor has been approved clinically, although different anti cancer drugs are in use that indirectly affect the HIF-1 pathway. Due to its central role in supporting growth and metastasis of tumor cell, it is

promising that in near future specific HIF-1α inhibitors will be developed and clinically approved.

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