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Brief Review

Hypoxia Inducible Factor-1α (HIF-1 α) and its Role in Tumour Progression to Malignancy

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Abstract:
Hypoxia is a condition in which an area of the body or a tissue is deprived of sufficient supply of oxygen. The lack of nutrients in a hypoxic tissue generally causes apoptosis but some cells are able to adapt to this hypoxic environment and resist apoptosis. This adaptation occurs as a result of gene activation. Hypoxia is a characteristic feature of many cancers and is the stimulus for overexpression of HIF-1α - a basic loop-helix PAS protein family subunit of HIF, which allows the cell to adapt and survive in hostile environment. The presence of hypoxia and HIF-1α is correlated with an increased risk of metastasis and techniques that can inhibit hypoxia inducible factor may be instrumental in finding a cure for cancer.
Key Words: HIF, HIF-1α, Hypoxia, Malignancy, Cancer, Cancer Therapy

Hypoxia:

Oxygen is one of the most vital requirements for normal functioning of our body and in healthy tissues rich vascular bed takes due care of this supply. In tumours however, the supply of oxygen can be compromised by haphazard arrangement of tissue cells which invade and compress blood vessels.

In addition to this, the angiogenic factors secreted by tumours lead to the growth of new blood vessels which are tortuous and leaky and do not respond to physiological signals that normally regulate blood flow.(1)

The chaotic arrangement of tumour tissue and its associated malformed blood vessels encourage the occurrence of hypoxia, a condition in which an area of the body or a tissue is deprived of sufficient supply of oxygen.

HIF 1:

The lack of nutrients in a hypoxic tissue generally causes apoptosis but some cells are able to adapt to this hypoxic environment and resist apoptosis

Hypoxia Inducible Factor-1 (HIF-1) which allows the cell to adapt and survive in hostile environment coordinates the response to hypoxia in normal as well as tumour tissues - in which hypoxia is many times the characteristic feature. HIF-1 mediates response in the heart and vascular system by activating gene transcription (2) for glucose transporters, glycolytic enzymes(3), and vascular endothelial growth factor (VEGF).

HIF 1α :

HIF-1 consists of two sub-units - HIF-1α and HIF-1β - both of which belong to the basic loop-helix Per-Aryl hydrocarbon nuclear translocator-Sim (PAS) protein family (4). Of the two subunits of Hypoxia Inducible Factor-1, HIF-1α plays a major role in determining its activity and increasing the survival of cell in the hypoxic environment by adaptive mechanisms(4).

Cancer Therapy and Drugs:

HIF-1α overexpression is associated with poor prognosis and resistance to therapy in high as well as low grade tumours in most cancers (5). As such, targeting HIF-1 mediated pathway by inhibiting HIF stability or transactivation, or inhibiting different steps in the signalling pathway downstream from HIF can lead to development of efficient anticancer therapies (6).

This review looks at scientific literatures, which have focused on the investigation and research of the role of HIF-1α in the progression of tumours to malignancy.

HIF-1α and *in vitro* studies:

Jenson et al (7) performed a study to establish a correlation between HIF-1α and malignant glioma phenotype by examining the expression of HIF-1α and its downstream-regulated proteins in glioma specimens of variable tumour grading. 175 human glioma specimens were obtained and graded according to WHO classification (Table 1). 114 (66%) of the tumors were classified as malignant gliomas with 22 glioblastoma tumors being recurrent tumors that had received prior radiotherapy.

Classification	Malignant			Low grade	
Tumor type	GBM	AO	AA	Low grade	Oligodendroglioma
Patients	94 (54%)	8 (5%)	12 (7%)	34 (19%)	27 (15%)
		114 (66%)		61 (34%)	
Age					
Mean (yrs)	60	38	46	35	47
		57		39	
Range (yrs)	24–81	29–46	30–71	18–78	23–73
		24–81		18–78	
Sex					
Male	62	3	6	18	12
		71 (62%)		30 (49%)	
Female	32	5	6	16	15
		43 (38%)		31 (51%)	

Table 1: Tumour grading in patients with glioma. AO: anaplastic oligodendrogliomas; AA: anaplastic astrocytomas(4)

The frequency of immunohistochemical positivity for HIF was higher in malignant gliomas (GBM, AA, and AO) than in lower grade tumors (astrocytomas and oligodendrogliomas).(7)

On the basis of these results the authors implied that HIF plays a critical role in malignant progression of the tumour. However many factors seemed to have been overlooked. Firstly, it should be noticed that these two tumour groups had unequal number of specimens with two thirds of specimens coming from high-grade gliomas.

Secondly, the specimens were obtained from dissimilar populations - the mean age for malignant gliomas was 57 with 62% being male compared with mean age of 39 and 49% males in low-grade tumour group.(7) A paper by Min et al (8) discusses that aging process induces the activation of HIF-1 and its downstream-regulated proteins like Vascular Endothelial Growth Factor (VEGF). Therefore, the comparison between high-grade tumours from an older aged population and low-grade tumours from relatively younger population in the study done by Jensen et al (7) may have introduced confounding in the results which was not dealt with.

And thirdly, even though a correlation can be established between the presence of HIF-1α and malignancy, it cannot be explicitly said just on the basis of these results alone that the latter arises as a result of the former. The results merely show the presence of HIF-1α in malignant tissues.

But another similar study done by Zhong et al (9) in which sample size and age confounding were taken care of, also used immunohistochemistry to analyze 179 tumour specimes and resulted in similar findings of HIF-1α overexpression in 13 metastatic tumour types.

HIF-1α and *in vivo* studies:

In the second part of the investigation Jensen et al (7) transfected Wild Type (WT) HIF-1α plasmid vectors in some glioma cells while others were transfected with Dominant Negative (DN) HIF-1α which inhibited HIF-1α production. These cells were grown on flanks of nude mice with empty vectors acting as control. The DN transfected cells showed a decreased growth trend in contrast to WT transfected cells.(7) However the results did not show a steady statistical variation in size of the tumor over time.

The investigation was repeated with the use of siRNA constructs to inibit the functioning of HIF-1α. In vivo studies, as above were done on mice with cells transfected with either HIF-1 shRNA or control shRNA. Statistically significant results were obtained this time which showed transfectants expressing shRNA had decreased HIF-1 activity and decreased growth compared with the control transfected cells (Figure 1).

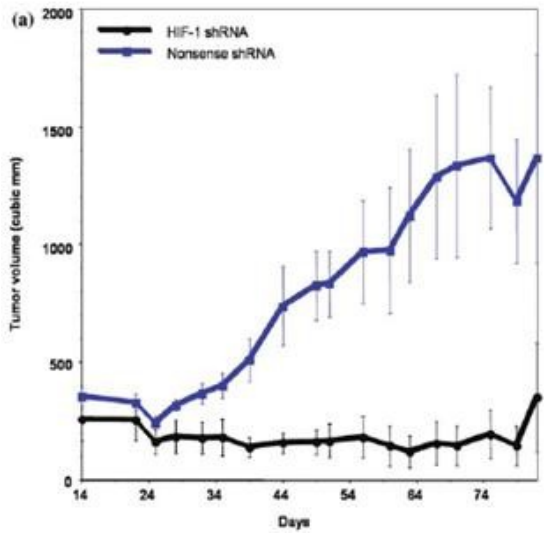

Figure 1 (4): Transfectants expressing shRNA (black line) had decreased HIF-1 activity and decreased growth compared with the control transfected cells (blue line)

The results of this study supported Turner et al's (10) findings that HIF-1α and VEGF are overexpressed due to mutation in von Hippel-Lindau tumour suppressor protein (vHL) gene which has been linked with the development of renal tumours into clear cell renal cell carcinomas (CC-RCC).

Conclusions:

A number of studies have found a correlation between the overexpression of HIF-1α and degree of growth of tumours in various tissues using HIF-1α knock-down or knock-out cancer cells.(11) The paper by Jensen et al (7) looked at this using both *in vitro* and *in vivo* techniques. Even though their *in vitro* results were beset by confounding, their results were replicated in another study(9) which also established a correlation between HIF-1α and tumour grading.

It has been consistently shown that vHL and p53 mutations are present in tissues with high levels of HIF-1α.(9) In order for tumours to metastasise, Warburg effects (12) of angiogenesis and increased glycolysis are crucial. The activation of these events has been shown to be mediated by HIF-1α.

The *in vivo* results from mice models from the study where tumour growth was restricted after HIF-1α inhibition emphasised the credible link between HIF-1α and the progression of tumours to malignancy as shown in other studies.

This has important implications for development of novel therapies that can inhibit HIF-1 activity and prevent the progression to malignancy thereby improving the prognosis of cancer survival.

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