Hypoxia-inducible factor 1 (hif-1) in cancer

P.A. Brennan\textsuperscript{a,\*}, N. Mackenzie\textsuperscript{a}, M. Quintero\textsuperscript{b}

\textsuperscript{a}Department of Oral and Maxillofacial Surgery, Queen Alexandra Hospital, Portsmouth PO6 3LY, UK
\textsuperscript{b}Wolfson Institute for Biomedical Research, The Cruciform Building, University College London, London, UK

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Summary
Hypoxia is a common feature of many cancers. It contributes to local and systemic tumour progression as well as potentially compromising radiotherapy and chemotherapy. Hypoxia-inducible factor 1 (HIF-1) is an essential component in changing the transcriptional response of tumours under hypoxia. It targets the transcription of over 60 genes involved in many aspects of cancer biology including cell survival, glucose metabolism, cell invasion and angiogenesis. Over-expression of HIF-1 has been associated with increased patient mortality in several cancer types including breast, stomach, cervical, endometrial and ovarian cancers. The pharmacological manipulation of HIF-1 has marked effects on tumour growth, and it could prove to be an important target for drug therapy, both in cancer and in other hypoxia-dependent disease states.

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Introduction

Tumour hypoxia is a common feature of many cancers and essentially occurs when the growth of the tumour outstrips the accompanying angiogenesis. All cells must be within 1–2 mm\textsuperscript{3} of a blood supply for survival.\textsuperscript{1} It is therefore not surprising that many parts of a developing tumour are hypoxic. Clinically, hypoxia may be deleterious by compromising the effects of radiotherapy\textsuperscript{2} and/ or chemotherapy.\textsuperscript{3} The transcriptional factor hypoxia-inducible factor 1 (HIF-1) plays an essential role in the adaptive response of cells to reduced oxygen tension.\textsuperscript{4} It functions as a master regulator of oxygen and undergoes conformational changes in response to varying oxygen concentrations.\textsuperscript{5}

Basic biology

HIF-1 consists of α and β-subunits which are both helix-loop-helix transcription factors. These subunits exist as a series of isoforms encoded by distinct genetic loci. The β-subunit is constitutively expressed and its’ activity is controlled in an oxygen independent manner. Expression of the α-subunit is induced by cellular hypoxia and is maintained at low levels in most cells with normal oxygen tension.\textsuperscript{6} The levels of HIF-1α are the primary determinant of HIF-1 DNA binding and transcriptional activity.\textsuperscript{7} The induction of HIF-1α is a critical step in the hypoxic response and occurs via increased mRNA expression, protein stabilisation, and nuclear localisation. Nuclear accumulation of HIF-1α protein can be detected with immuno-histochemistry and occurs not only in human cancers\textsuperscript{8–10} but also in conditions such as myocardial infarction.\textsuperscript{11}

More than 60 target genes that are activated by
HIF-1 have been identified (for review see Ref. 12). These include genes encoding for vascular endothelial growth factor (VEGF), erythropoietin, and many enzymes involved in glucose, iron, and nucleotide metabolism. VEGF is the most potent endothelial-specific mitogen known and several studies have demonstrated it to have a central role in angiogenesis. HIF-1 can be viewed as a messenger that is sent from the cytoplasm to the nucleus to activate transcriptional responses to hypoxia. A simplified representation of the processes influenced by HIF-1 is shown in Fig. 1.

**Other HIF proteins**

In addition to HIF-1α and β, two other proteins have been identified. These are additional α isoforms termed HIF-2α and HIF-3α. HIF-2α is closely related to HIF-1α and both are able to interact with hypoxia response elements to upregulate transcriptional activity. By contrast HIF-3α is involved in downregulation of the hypoxic response via an alternatively spliced transcription factor, which may function as an inhibitor of HIF-1α.

**Effects of HIF-1 in human cancers**

A wide range of other physiological and pathological pathways activate the HIF system. Growth promoters including insulin, insulin-like growth factor and epidermal growth factor amplify the system together with the oncogenes Ras and Myc. Mutations in tumour suppressor genes such as p53 and pVHL also lead to induction and amplification of the HIF system. Most cancers over-expressing HIF-1 are associated with increased mortality. In experimental models, HIF-1 depletion severely impedes tumour growth and angiogenesis. Adverse effects on patient survival are found in cervical, breast, ovarian, endometrial, and stomach cancers. However, conflicting results relating to the over-expression of HIF-1α in head and neck cancers and non small-cell lung cancers found either increased mortality or decreased mortality. These differing results may perhaps be explained by the interaction of HIF-1α with genes involved in apoptosis such as p53 and the Bcl-2 family. The effect of HIF-1α expression in individual cancers seems to be dependent on the specific cancer type as well as the presence or absence of genetic alterations that affect the balance between either pro or anti-apoptotic effects.

Although HIF-1 expression is related to the degree of hypoxia, it is additionally overexpressed by hypoxia independent pathways, such as glucose deprivation and oncogene activation. Cancer development is known to be the result of...
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In most human cancers, HIF-1α expression seems to be associated with tumour progression and development. Hypoxic cancer cells are also more likely to be resistant to radiotherapy and chemotherapy, and interestingly, HIF-1 itself mediates resistance to both radiotherapy and chemotheraphy. Therefore, inhibition of HIF-1 activity might enhance existing radiotherapy and chemotherapy regimes. By reducing the angiogenic affect, it may reduce tumour growth and dissemination. Over-expression of HIF-1α is associated with radiation resistance and increased mortality regardless of tumour grade, stage or other biomarkers in head and neck cancer.

A number of novel therapeutic agents are being developed by the National Cancer Institute (NCI) Developmental Therapeutic Program. These include the agents 17-AAG, which induces HIF-1α degradation acting via heat shock protein (HSP 90). Another agent, 2-methoxyestradiol (2ME2) has also been shown to reduce HIF-1α levels by disrupting microtubule polymerisation. There are a number of other inhibitor drugs also undergoing clinical trials although it seems that none of these specifically target HIF-1.

Conversely, drug-associated HIF-1 induction may be useful in pathologies associated with hypoxia such as myocardial infarction and other diseases associated with vascular occlusion.

Conclusions

By acting on a large number of target genes, HIF-1 seems to facilitate both cancer growth and spread in the majority of human cancers. It may also reduce the efficacy of existing radiotherapy and chemotherapy regimes. The therapeutic targeting of HIF-1 is an exciting area for possible therapy, and the results of clinical trials are awaited with interest.

References

16. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME et al. The tumor suppressor protein VHL targets...
hypoxia inducible factors for oxygen dependent proteolysis.


