Nature Reviews Urology published online 1 July 2014; doi:10.1038/nrurol.2013.110-c2

Normoxic regulation of HIF-1α in prostate cancer

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The hypoxic microenvironment of tumours, acting via hypoxia inducible factor 1α (HIF-1α), might promote the angiogenic stimulation required for cancer development, with a resultant aggressive cell phenotype and rapid malignant progression.[1] In their recent article, Marignol *et al.*[2] described the importance of notch signalling pathways in differentiation, proliferation, angiogenesis, vascular remodelling and apoptosis in prostate cancer (Marignol, L., Rivera-Figueroa, K., Lynch, T. & Hollywood, D. Hypoxia, notch signalling, and prostate cancer. *Nat. Rev. Urol.* **10**, 405–413; 2013). The Review highlighted similarities between notch-activated and hypoxic prostate cancer cells. We believe that normoxic HIF-1α expression in prostate cancer, is equally important to—if not more important than—hypoxia mediated by HIF-1α. Indeed, a better understanding of the former would lead to improved prognostication and, potentially, reduced treatment resistance in men with this disease.

Although HIF-1α has a key role in the physiological response to hypoxia, its importance in cancers is less clear. High expression of HIF-1α in some cancer cell lines (for example, renal and breast cancers) has been shown to increase angiogenesis and cancer cell survival, whereas in other cancers (such as ovarian carcinoma), high HIF-1α concentrations contribute to increased apoptosis.[3] In prostate cancer, HIF-1α overexpression has been linked with shorter time to biochemical recurrence in patients receiving radiotherapy or surgery, castration resistance, chemoresistance and metastasis.[4–6] Although hypoxia is a strong driver of HIF-1α expression, and the presence of hypoxic regions has been shown in many human tumours, the localized expression of HIF-1α and its downstream targets only in the hypoxic areas of tumours has been difficult to demonstrate.[7] Furthermore, it has been consistently difficult to demonstrate localized hypoxia, particularly in high-grade prostate cancer; consequently, HIF-1α expression is thought to be independent of hypoxia.[8]

HIF-1α expression can be upregulated independently of hypoxia by many factors, including oncogenes, growth factors and free radicals. Indeed, expression of HIF-1α is consistently higher in prostate cancer, benign conditions (for example, BPH) and precancerous conditions, than in normal prostate tissue.[9] Several different hypotheses, including gene amplification,[10] increased transcription of HIF-1α mRNA,[11] single nucleotide polymorphisms[12] and expression of truncated HIF-1α isoforms[13] have been proposed to explain the overexpression of HIF-1α in prostate cancer tumours and cell lines under normoxic conditions. However, as yet no definitive consensus can explain the mechanisms involved.

In addition to the widely accepted mechanism of hypoxia-induced post-translational stabilization of HIF-1α by decreased degradation, current evidence suggests that the hypoxia-independent normoxic upregulation of HIF-1α expression can occur by increased translation. In prostate cancer cell lines, overexpression of HIF-1α protein under normoxic conditions is probably attributable to the increased efficiency of translation of the corresponding mRNA,[6] which might be mediated by the PI3K/Akt/mTOR pathway.[14] Whether the increased translation of HIF-1α occurs via cap-dependent or cap-independent pathways remains to be determined. Thus, understanding which of these translation mechanisms leads to upregulation HIF-1α overexpression in normoxia could lead to future targeted therapy for prostate cancer.

As HIF-1α has a central role in the activation of numerous pathways responsible for tumour progression, it has become an attractive target for cancer therapy. Various different types of inhibitors have been developed, including inhibitors of HIF-1α dimerization, HIF-1α DNA binding, HIF-1α transcription, small molecules that affect the HIF-1α protein level and natural product-based inhibitors.[15] HIF-1α regulates many normal physiological processes and an agent that inhibits HIF-1α might prevent normal cells from responding to a situation (such as hypoxia) that might be associated with toxicity. Thus, we believe that a better understanding of the normoxic regulation of HIF-1α in prostate cancer cells could direct the discovery of specific HIF-1α inhibitors that could then potentially lead to therapies better targeted against treatment resistance, and will provide better outcomes for men with prostate cancer.

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Competing interests
The authors declare no competing interests.

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