HIF1α Expression under Normoxia in Prostate Cancer—Which Pathways to Target?

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Purpose: HIF1α over expression correlates with poor prognosis in a number of cancers. Although it is widely accepted that hypoxia induces HIF1α expression up-regulation by a reduction in oxygen dependent degradation, HIF1α up-regulation under normoxic conditions is noted with increasing frequency in many cancers. We reviewed the current knowledge of mechanisms of normoxic and hypoxic HIF1α up-regulation, and its therapeutic implications with a particular focus on its role as a potential biomarker in prostate cancer.

Materials and Methods: Although the literature on the role of HIFs in cancer development and progression has been reviewed extensively, few publications have specifically considered the role of HIFs in prostate cancer. Therefore, we searched PubMed® and Google® with the key words prostate cancer, castration resistance, metastasis, hypoxia, HIF1α, HIF2α and regulation. Relevant articles, including original research studies and reviews, were selected based on contents and a synopsis was generated.

Results: Normoxic expression of HIF1α has an important role in the development of prostate cancer chemoresistance, radioresistance and castrate resistance. Thus, HIF1α could serve as a potential biomarker. Furthermore, agents that target HIF1α could be used as adjuvant therapy to decrease resistance to conventional treatment modalities. HIF1α over expression in prostate cancer can be regulated at 3 levels, including transcription, translation and protein stability, by a number of mechanisms such as gene amplification, single nucleotide polymorphism, increased transcription of HIF1α mRNA, expression of truncated isoforms of HIF1α and stabilization of HIF1α. However, there is no definitive consensus and the intriguing question of how HIF1α is up-regulated in prostate cancer is still unanswered.

Conclusions: HIF1α over expression under normoxia could serve as a biomarker for chemoresistance, radioresistance and castrate resistance in prostate cancer. There is an urgent need to identify the cause of HIF1α over expression in castrate resistant prostate cancer cells and tumors to guide the choice of HIF inhibitors (transcription or translation based) that are best suited for treating castrate resistant prostate cancer.

Key Words: prostatic neoplasms, castration-resistant; hypoxia-inducible factor 1, alpha subunit; up-regulation; anoxia; biological markers

Abbreviations and Acronyms

4E-BP1 = eukaryotic translation initiation factor 4E binding protein

ADT = androgen deprivation therapy

AMPK = adenosine monophosphate-dependent kinase

CRPC = castration resistant PC

eIF = eukaryotic translation initiation factor

HIF = hypoxia-inducible factor

IDH-1 = isocitrate dehydrogenase-1

IRES = internal ribosome entry site

mTOR = mammalian target of rapamycin

PC = prostate cancer

PHD = prolyl hydroxylase

PI3K = phosphatidylinositol 3-kinase

VEGF = vascular endothelial growth factor

VHL = von Hippel-Lindau

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Androgens and androgen receptors are the main regulators of PC cell stimulation, growth and survival. Thus, endocrine therapy directed toward reducing serum androgens and inhibiting androgen receptors is the key tenet of treatment in men with advanced or metastatic PC. However, inevitably PC develops resistance to ADT and progresses to CRPC. Our understanding of the mechanisms that contribute to PC pathogenesis and resistance is currently limited and pathways related to HIF1α are being investigated as future therapeutic targets.

HIF1α triggers many adaptive survival mechanisms such as anti-apoptosis, angiogenesis and enhanced glycolytic metabolism.[1,2] HIF1α is a crucial transcription factor that acts as a potent tumor induced shield against injury from oxidative stress or destruction by androgen deprivation, chemotherapy or radiation cytotoxicity (fig. 1).[3] While initially noted for its actions in hypoxic conditions, HIF1α up-regulation under normoxic conditions has been noted in many cancers.

We reviewed current knowledge of the processes involved in normoxic and hypoxic HIF1α up-regulation with a particular focus on prognostic and therapeutic implications for PC. We also examined why targeted inhibition of downstream products of HIF1α such as VEGF has not shown the anticipated therapeutic benefits and which pathways might be better suited as future targets.

HIF1α STRUCTURE AND HYPOXIC REGULATION

The ability of cells to adapt to hypoxia depends on a set of hypoxia inducible transcription factors or HIFs, which bind to the core sequence 5′-RCGTG-3′ in target promoters. The number of HIF target genes currently exceeds 1,000.[4] HIFs consist of a regulatory α subunit (HIF1α) and a constitutive β subunit (HIF1β, also termed ARNT). Three forms of the α subunit (HIF1α, 2α and 3α) have been discovered but most transcriptional responses to HIF have been attributed to HIF1α and HIF2α.[5]

HIFs are modified in response to variations in oxygen tension by 2 indirect mechanisms (fig. 2). One mechanism, which has been reviewed in detail, is via 2-oxoglutarate and iron dependent PHDs.[2] PHDs hydroxylate the 2 prolyl residues Pro402 and/or Pro564 in HIF1α in the presence of oxygen. The hydroxylated prolines enable HIF1α to interact with VHL protein, a component of an E3 ubiquitin ligase complex first defined as a tumor suppressor. Subsequently HIF subunits become marked with polyubiquitin chains that direct them to degradation by the proteasomal system.[1] The second mechanism is via asparaginyl hydroxylase (originally referred to as factor inhibiting HIF1α), which in the presence of oxygen hydroxylates the asparagine residue at position 803 in HIF1α.[1] This modification prevents HIF1α binding to the transcription cofactors p300 and CBP, thereby inhibiting HIF1α mediated gene transcription. Therefore, under normal conditions the biological activity of the HIF1 complex is determined by changes in oxygen tension.

HYPOXIA AND HIF1α IN PROSTATE TUMORS

Normal cellular homeostasis depends on the delivery of adequate supplies of oxygen and various

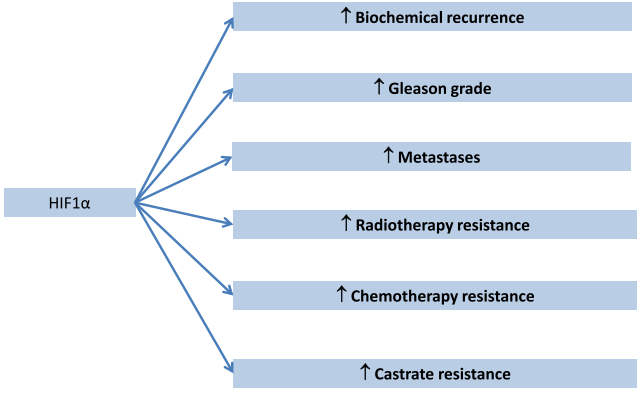

Figure 1. Increased HIF1α expression in PC is associated with increased metastasis, biochemical recurrence and chemoresistance. HIF1α induced castrate resistance mechanisms include up-regulation of alternate growth promoting pathways such as IGF-1, EGF and HER2 pathways, which may drive tumor growth independently of androgens.

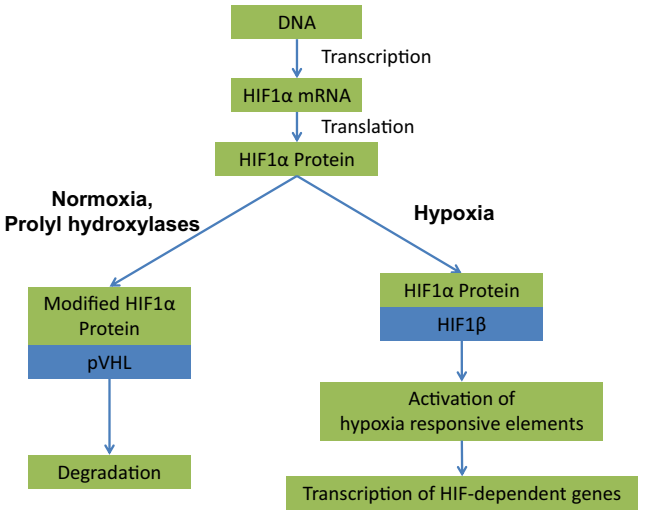

Figure 2. HIF1α protein degradation in normoxia is limited by formation of complex of modified HIF with VHL protein. Under hypoxic conditions HIF1α and HIF1β subunits combine and bind to hypoxia responsive elements in HIF dependent gene promoters to activate transcription.