HIF-α, a Gender Independent Transcription Factor

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Adenocarcinoma of the prostate is one of the most common cancers in the United States and is a leading cause of death in American men, despite recent progress in public education and early detection, and improvements in treatment delivery (1). Accepted clinical and biochemical prognostic factors for prostate cancer include prostate-specific antigen, Gleason grade, and clinical stage. Tumor hypoxia is a microenvironmental factor that has been shown to affect the malignant progression of transformed cells (2) and treatment outcomes in various solid tumors including prostate cancer (3–5). Radiobiological studies have suggested the existence of tumor hypoxia in prostate cancer xenografts (6), and Eppendorf partial oxygen pressure histogram measurements have demonstrated the existence of hypoxia in patient tumors (7, 8). The extent of tumor hypoxia appears to correlate with tumor stage and VEGF staining expression in the tumor tissues, and, more importantly, preliminary data indicate that the ratio of prostate to muscle pO2 can predict biochemical control in patients treated with brachytherapy for organ-confined disease (5, 7, 9). Androgenic steroids, which can stimulate tumor growth, are important regulators of blood flow in prostate cancers and thereby can also affect tumor oxygenation. For example, androgen deprivation of LNCaP tumor cells resulted in a significant decrease in VEGF expression (10). Similarly, patients with antiandrogen treatment before brachytherapy had much less tumor hypoxia than those without antiandrogen treatment (8). Taken together, these data raise the intriguing possibility that an important downstream effect of androgen deprivation may involve a change in tumor hypoxia and the expression of hypoxia-related genes.

A major cellular response to hypoxia is mediated through HIF-1, which is a heterodimeric protein that consists of a constitutively expressed aryl hydrocarbon receptor nuclear translocator (also known as HIF-1β) and a hypoxia-responsive element, HIF-1α. In the presence of oxygen, HIF-1α is hydroxylated by a family of prolylhydroxylases and subjected to rapid ubiquitination and proteasomal degradation mediated by the Von-Hippel Lindau-dependent pathway (11, 12). Under hypoxic conditions, hydroxylation is inhibited, resulting in the stabilization of HIF-1α protein, which translocates into the nucleus, dimerizes with HIF-1β, and activates hypoxia-responsive genes, many of which are important for cellular metabolism, proliferation, immortalization, apoptosis, angiogenesis, and migration (13). In addition to protein stabilization, the levels of HIF-1α protein can also be modulated through increased translation and transcription, although the latter is rarely observed. In prostate cancers, both genetic and environmental changes can result in HIF-1α protein stabilization. For example, the oxygen-dependent degradation domain of HIF-1α protein has been shown to harbor mutations in some prostate cancer specimens, and these mutations may result in stabilization of the protein under normoxia (14). In addition, the tumor suppressor gene PTEN, which negatively regulates the PI3-K pathway, is a common target for mutation in prostate cancers (15). Loss of PTEN function has been associated with increased angiogenesis and tumor progression in gliomas and prostate cancers, a phenomenon probably mediated in part by HIF-1α and VEGF (16, 17). Finally, stimulation of prostate cancer cells with a variety of growth factors and cytokines, including EGF, serum, and phorbol 12-myristate 13-acetate, induces the expression of HIF-1α protein, HIF-1 gene binding activity, and HIF-1 target gene expression under normoxic conditions. As shown by Mabjeesh et al. (18) in this issue of Clinical Cancer Research and shown previously by Zhong et al. (17), cytokine-mediated increase of HIF-1α appears to involve the PI3-K/AKT/FKBP12-rapamycin-associated protein pathway because it can be blocked by LY294002 (a PI3-K inhibitor), rapamycin (a FKBP12-rapamycin-associated protein inhibitor), or introduction of dominant-negative AKT or PI3-K genes or through overexpression of the wild-type PTEN gene (17). Mabjeesh et al. (18) also elegantly show that androgens, specifically dihydrotestosterone, increase HIF-1α expression and DNA binding activity under hypoxia, in androgen-sensitive prostate cancer cell line LNCaP but not in PC3, an androgen-resistant cell line. This effect was suppressible by the antiandrogens flutamide and bicalutamide. Stimulation of cells with dihydrotestosterone increased HIF-1α levels through de novo protein synthesis rather than protein stabilization, and the increased HIF-1α expression was mediated via a soluble factor secreted into the conditioned media by tumor cells. The authors hypothesized that EGF and EGFR may be the principal players in this paracrine/autocrine loop that is mediated by the PI3-K/AKT pathway because a similar increase in HIF-1α protein levels and activity was noted with EGF stimulation of cells, and this increase was blocked by EGF antibody or LY294002. Their data support a paracrine/autocrine model on how androgens affect HIF-1α protein expression and function. Whereas this model is useful in

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3 The abbreviations used are: VEGF, vascular endothelial growth factor; HIF, hypoxia-inducible factor; PI3-K, phosphatidylinositol 3′-kinase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; IGF, insulin-like growth factor.
explaining the cross-talk between androgen receptor activation and HIF-1α signaling, it is unlikely that EGF is the only growth factor involved in this autocrine/paracrine pathway. Laughner et al. (19) have showed that HER2-neu signaling that is induced either by genetic overexpression or by heregulin stimulation has a similar effect in increasing HIF-1α protein synthesis and DNA binding activity in breast cancer cell lines. Because HER2-neu is often overexpressed in hormone-refractory prostate cancers, it may also be an important signal for HIF-1α activation (20). Similarly, insulin and IGF-I have been shown to increase HIF-1 DNA binding activity and activation of HIF-1’s downstream targets (21). Thus, HER2-neu and IGF-I may also be candidate cytokines involved in this paracrine/autocrine pathway for HIF-1 regulation in prostate cancer.

Regardless of which growth factor is involved, Mabjeesh et al. (18) have proposed a novel mechanism for tumor progression in prostate carcinomas and a new approach for targeting these tumors. In early-stage prostate cancer, androgen stimulation is a dominant signal that affects the expression of cytokine- and hypoxia-mediated genes. Therefore, androgen blockade combined with local therapy is a reasonable initial treatment approach for these tumors. However, after prolonged castration, many patients relapse with hormone-refractory disease, and the progression from an androgen-sensitive to an androgen-insensitive tumor is associated with up-regulation of paracrine/autocrine loops involving several cytokines such as EGF, transforming growth factor α, and IGF (22, 23), many of which can fuel the activity of HIF-1α and its downstream genes. Preclinical studies have shown that EGFR overexpression is common in patients with hormone-refractory metastatic disease (20). Studies have shown that the blockade of EGFR with either monoclonal antibody IMC-C225 or an antisense oligonucleotide to transforming growth factor α can inhibit tumor growth and metastasis in hormone-refractory xenograft models (24, 25). However, it is as yet unknown how effective this approach will be in patients. In summary, the data suggest that blockade of different receptor tyrosine kinases such as EGFR or HER2-neu or the inhibition of the PI3-K pathway either alone or in combination with conventional therapy is a rational approach to tackling advanced hormone-refractory prostate cancers. This recent study by Mabjeesh et al. (18) also indicates an important role for HIF-1α inhibition in prostate tumors. Therapeutic strategies using one or a combination of these targeted therapies should be considered in future clinical trials for these incurable cancers.

REFERENCES


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