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The role of Eph A receptor 3 tyrosine kinase signaling in prostate cancer progression

Short Title:
EPHA3 signaling in prostate cancer

Author Block: Marwah M. Al-Mathkour, Bekir Cinar. Clark Atlanta University, Atlanta, GA

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Dysregulation of the receptor tyrosine kinases (RTKs) by means of mutation, amplification or overexpression plays a crucial role in cell growth, cell survival, cell motility during cancer progression and metastasis. EPHA3 (erythropoietin-producing hepatocellular carcinoma cell surface type A receptor 3) is a member of the RTKs. Evidence indicates that the upregulation of the EPHA3 activity is implicated in the pathobiology of various cancers, including prostate cancer, and thus, it is a prime therapeutic target in cancer. However, the role of EPHA3 signaling in prostate cancer progression remains obscure. Currently, the development of castration-resistant prostate cancer (CRPC) poses a clinical challenge because it is lethal. The molecular mechanisms that contribute to lethal prostate cancer are largely unknown. The objective of this study is to investigate whether EPHA3 signaling plays a critical role in prostate cancer progression and therapeutic relapse. Our analysis of the prostate cancer public datasets revealed that the EPHA3 gene was amplified up to 19% of metastatic CRPC cases with the neuroendocrine phenotype. Our immunological assay confirmed the positive staining of EPHA3 protein in human prostate cancer specimens. Our semi-quantitative and quantitative PCR assays demonstrated that the levels of EPHA3 varies among established prostate cancer cell lines. Nevertheless, we consistently found that the levels of EPHA3 mRNA in CRPC cell line, C4-2, were 3-fold higher than its castration-sensitive parental LNCaP cells. Furthermore, we demonstrated that increase in expression of EPHA3 mRNA in C4-2 compared with LNCaP cells coincided with the upregulation of the EPHA3 protein, as independently confirmed by western blotting and immunofluorescence imaging. These findings indicate that EPHA3 may confer an aggressive prostate cancer cell phenotype. Because androgen receptor (AR) signaling is a potent mediator of CRPC cell growth and survival, the targeting of EPHA3 signaling alone or together with AR may improve the efficacy of current therapies for patients with advanced prostate cancer.
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Author Disclosure Information:

M.M. Al-Mathkour: None. **B. Cinar:** None.
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