ECTOPIC OVER EXPRESSION OF ARYL HYDROCARBON RECEPTOR (AHR) INDUCES ANDROGEN INDEPENDENT SIGNALING IN LNCAP PROSTATE CANCER CELL LINE

Maryam Ghotbaddini and Joann B. Powell

Center for Cancer Research and Therapeutic Development, Clark Atlanta University, 223 James P. Brawley Drive Atlanta, Georgia, USA

Abstract: The aryl hydrocarbon receptor (AhR) is a member of the basic-helix-loop-helix family of transcription factors. AhR is widely known for regulating the transcription of drug metabolizing enzymes involved in the xenobiotic metabolism of carcinogens and therapeutic agents, such as cytochrome P450-1B1 (CYP1B1). Additionally, AhR has also been reported to interact with multiple signaling pathways during prostate development. Here, we investigate the effect of ectopic over expression AhR on androgen receptor function in androgen sensitive LNCaP prostate cancer cells. AhR was overexpressed in the LNCaP cell line using PLNCX2 retrovirus vector containing AhR cDNA. Western blot analysis revealed higher AhR, AR, cSrc and pSrc protein expression in the clone A and B compare to the control. qRT-PCR was used to determine mRNA expression of AhR responsive genes, CYP1B1 and CYP1A1, as well as androgen responsive genes, KLK2 and KLK3. The highly overexpressed AhR cell line, clone B, showed further increase in gene expression for all transcripts compare to clone A (a moderately overexpressed AhR clone) and the PLNCX2. Both androgen responsive element binding assays and xenobiotic responsive element binding assays confirmed that clone A and clone B significantly increase AR and AhR DNA binding compared to control. In addition, treatment with bicalutamide has no effect on AR signaling patterns in either Clone A or Clone B. Cell proliferation studies revealed a significant increase in the growth rate of both clones that correlates to AhR activity. Overexpression of AhR was also found to promote G1 to S phase cell cycle transition. Our results confirm that overexpression of AhR induces constitutive activity. Furthermore, constitutive AhR activity can stimulate androgen receptor signaling and mediate growth. The results suggest a role for AhR in the development of castration resistant prostate cancer (CRPC). Future studies may establish AhR as a therapeutic target for ablation of androgen receptor signaling in CRPC.

Key Words: AhR, prostate cancer, androgen signaling, castration resistant prostate cancer

Acknowledgements: These studies were supported by the RCMI grant # 8 G12 MD007590-NIH/National Institute on Minority Health and Health Disparities (NIMHD) Grant # 5 G12 RR003062.