INHIBITION OF CONSTITUTIVE ARYLY HYDROCARBON RECEPTOR (AhR) SIGNALING ATTENUATES ANDROGEN INDEPENDENT SIGNALING AND GROWTH IN PROSTATE CANCER CELLS

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Abstract: The aryl hydrocarbon receptor is a member of the basic-helix-loop-helix family of transcription factors. AhR mediates the biochemical and toxic effects of a number of polyaromatic hydrocarbons such as 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). 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 sustained AhR signaling on androgen receptor function in prostate cancer cells. Immunoblot analysis shows that AhR expression is increased in androgen independent (C4-2) prostate cancer cells when compared to androgen sensitive (LNCaP) cells. RT-PCR studies revealed constitutive AhR signaling in C4-2 cells without the ligand induced activation required in LNCaP cells. A reduction of AhR activity by short RNA mediated silencing in C4-2 cells reduced expression of both AhR and androgen responsive genes. The decrease in androgen responsive genes correlates to a decrease in phosphorylated androgen receptor and androgen receptor expression in the nucleus. Furthermore, the forced decrease in AhR expression resulted in a 50% decline in the growth rate of C4-2 cells. These data indicates that AhR is required to maintain hormone independent signaling and growth by the androgen receptor in C4-2 cells. Collectively, these data provide evidence of a direct role for AhR in androgen independent signaling and provides insight into the molecular mechanisms responsible for sustained androgen receptor signaling in hormone refractory prostate cancer.

Key words: Dioxin, TCDD, AhR, androgen receptor, progression

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