ARYL HYDROCARBON RECEPTOR (AhR) SIGNALING INDUCES HORMONE INDEPENDENT PROSTATE CANCER CELL PROGRESSION THROUGH ENHANCEMENT OF ANDROGEN RECEPTOR SIGNALING

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Abstract: The five year survival rate for men diagnosed with local or regional prostate cancer is 100%. However, men diagnosed with a distant metastasis have a five year survival rate of just 29%. Most men who die of prostate cancer present with hormone refractory prostate cancer (HRPC). Early stage prostate cancers are dependent on androgens for growth. Therefore, androgen deprivation therapy (ADT) is the predominant form of treatment. However, tumors recurring following ADT, termed HRPC, no longer respond to hormone therapy despite evidence showing that androgen receptor signaling still plays a major role. The molecular mechanisms responsible for sustained androgen receptor signaling in HRPC are not clearly understood. The aryl hydrocarbon receptor (AhR) affects a number of biological processes including cell growth and differentiation. Several studies have revealed that exogenous AhR ligands inhibit cellular proliferation but recent evidence suggests AhR may possess intrinsic functions that promote cellular proliferation in the absence of exogenous ligands. Despite the protective effects against tumor initiation seen with specific ligand activation of AhR, studies concerned with intrinsic functions of AhR have found that AhR protein and mRNA expression is associated with phases of rapid proliferation and differentiation in certain tissues. Additionally, AhR-defective cell lines demonstrate a reduced proliferation rate. Ectopic over expression of AhR in immortalize mammary epithelial cells induced a malignant phenotype with increased growth and acquired invasive capabilities. Independent experiments utilizing a constitutively active recombinant AhR construct lacking the ligand binding domain demonstrated AhR’s ability to act as a co-regulator for unliganded estrogen and androgen receptor. Research from our lab shows that AhR is overexpressed and constitutively active in advanced prostate cancer cells. Constitutive/ligand-independent AhR signaling may prove to be a vital factor in progression of prostate cancer from hormone sensitive to hormone refractory.

Keywords: AhR, androgen receptor, progression, hormone refractory prostate cancer

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