TARGETING OF ARYL HYDROCARBON RECEPTOR (AhR) SIGNALING IN ADVANCED PROSTATE CANCER

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Abstract: Prostate cancer is the most common cancer in American males and the second leading cause of cancer related death behind lung cancer. When caught early, prostate cancer is often cured with radiation, surgery or both. African American men are 60% more likely than white men to be diagnosed with prostate cancer during their lifetime and are more than twice as likely to die from the disease. Black men are also diagnosed at a younger age and present with higher grade tumors at the time of diagnosis. Recent studies demonstrate that for men with clinically localized, non-metastatic high-risk prostate cancer receiving long-term androgen deprivation therapy (ADT) and dose-escalated radiotherapy (RT), a pre-RT PSA value greater than 0.5 ng/ml after ADT predicts for decreased time to distant metastases and a decrease in overall survival. In these studies, African-American men were significantly associated with failure to achieve a pre-RT PSA value less than 0.5 ng/ml. These elevated PSA levels are a direct result of sustained androgen receptor signaling despite ADT. African-American men would benefit greatly from more potent anti-androgenic therapies in combination with radiation. 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 CRPC, 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 CRPC are not clearly understood. Additional studies are needed to identify all modulators of androgen receptor signaling to develop targeted therapeutic strategies. Our studies provide novel insight into androgen-independent signaling and aim to establish the aryl hydrocarbon receptor (AhR) as a key player in CRPC. AhR is a cellular protein that is well studied for mediating the carcinogenic responses to environmental toxins. Currently accepted understanding states that AhR requires direct binding by environmental toxins to elicit its effects. However, our data demonstrates that AhR may promote cancer progression independent of ligand binding by environmental toxins. The broad objective of these studies is to prove that constitutive/ligand independent AhR activity induces androgen independent signaling and progression of prostate cancer.

Key words: AhR, androgen receptor, progression, castration resistant prostate cancer

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