Heterogeneous Nuclear Ribonucleoprotein H1 Confers Transcription and Transactivation of Androgen Receptor: Implications for Disease Progression in African American Men

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Introduction: African American men (AA) have twice as high the incidence and mortality of prostate cancer (CaP) than Caucasian American (CA) and other ethnic minority groups. The causes of this ethnic disparity in clinical manifestation and outcome of the disease are not well understood.

Materials and Methods: We identified, by employing a combined approach of laser capture microdissected (LCM), suppressive subtractive hybridization (SSH), and custom race-based CaP cDNA microarray on fresh specimens, selective expression of heterogeneous nuclear ribonucleoprotein H1 (hnRNPH1) in prostate tumor cells of AA men in comparison to CA men. An ethnicity-based tissue microarray (TMA) analysis revealed selective nuclear accumulation of hnRNPH1 in tumor cells compared to adjacent normal epithelium and benign prostatic hyperplasia (BPH).

Results: In addition to selective expression, hnRNPH1 up-regulates transcription, physically interact with, and confers hormone-dependent (HD) and independent (HI) transactivation of androgen receptor (AR) in CaP cells. Further, our reporter, ChIP, and EMSA analyses demonstrate hnRNPH1 binds to androgen response elements (AREs) on promoter and enhancer element of PSA gene and the ligand binding domain-encoding exons D, E and H of the AR gene, suggesting it acts as a coactivator of AR in CaP cells. Interestingly, siRNA silencing of hnRNPH1 caused growth arrest and enhanced cytotoxicity of Bicalutamide in AR-expressing PC cells.

Conclusions: Our findings support a model in which hnRNP H1 is an exclusive auxiliary factor for AR to elicit androgen-specific transcriptional regulation of androgen-regulated genes and development of drug resistance. Given heterogeneity of CaP and that AR is implicated in androgen independent progression of CaP, the results demonstrate a previously uncharacterized mechanism for AR-hnRNPH1 axis in disease progression and hormone refractory via enhancing HD and HI mediated transcription and transactivation of AR in a subset of prostate tumor cells in AA men. The results not only reveal racial differences in the biology of PC, but also provide, for the first time, a new frontier for the development of diagnostic, preventive, and/or targeted therapeutic strategies to circumvent disease progression in AA men.