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Analysis of A Novel Nonsense Mutation of Androgen Receptor Gene in Castration-Resistant Prostate Cancer

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BACKGROUND: Prostate cancer (PCa) is the second leading cause of cancer mortality in American men. The standard treatment for PCa is androgen deprivation therapy (ADT) that blocks transcriptional activity of androgen receptor, but ADT invariably leads to the development of castration-resistant form of PCa (CRPC) with restored activity of AR. CRPC can be further treated with more intensive ADTs, including CYP17-inhibitors to block intratumoral androgen synthesis and more potent AR antagonist (enzalutamide). Most CRPC patients still relapse after a year of treatment and AR activity appears to be restored again. By analyzing the tumor mRNA from a CRPC patient biopsy who had developed resistance to CYP17-inhibitor treatment, we identified a novel nonsense AR mutation on ligand binding domain (Q784sc), which presumably produces a C-terminal truncated form of AR protein that lacks ligand binding domain (LBD) and may mimic certain AR splice variants that also lack LBD. We thus hypothesized that AR-Q784sc mutant may gain the androgen-independent activity or may enhance the transcriptional activity of full-length AR under low androgen environment through dimerization with full-length AR.

METHOD: We utilized luciferase reporter assays to assess the activity of AR-Q784sc in absence or presence of androgens, and with/out full-length AR. We also examined the protein stability and cellular localization of AR-Q784sc using immunoblotting and immunofluorescence. Moreover, stable cell lines that overexpress AR and/or AR-Q784sc were generated to assess the transcription activity on endogenous target genes and on PCa cell growth.

CONCLUSION: AR-Q784sc mutant produces a LBD truncated AR protein that does not have any transcriptional activity by it alone. However, AR-Q784sc can significantly enhance transcriptional activity of full-length AR though dimerization, indicating that the more intensive ADTs may allow CRPC cells to select for LBD truncated form of AR to further enhance the full-length AR activity under low androgen environment.

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