Targeting Hippo-YAP/TAZ-TEAD signaling as a therapeutic vulnerability in castration-resistant prostate cancer

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Background: YAP/TAZ-TEAD signaling is frequently upregulated in prostate cancer (PCa) and contributes to therapy resistance, especially in castration resistant prostate cancer (CRPC). Given the growing interest in small-molecule inhibitors targeting this pathway, our study examines the efficacy of Hippo-YAP/TAZ–TEAD inhibition in enzalutamide-resistant PCa models.

Methods: LNCaP, PC3 and DU145 cells were obtained from ATCC. LNCaP and C4-2 cells were cultured with enzalutamide (5 μM) for more than six months to generate enzalutamide resistant lines (LNCaP-ENZR (PCaNO1), and C4-2-ENZR (PCaNO2) cells respectively). Specific mRNA levels were quantitated by Real-time PCR. Protein levels were assessed via western blotting. The anti-tumor effects of YAP/TAZ–TEAD inhibitors (GNE-7883, K-975) were evaluated using live-cell imaging (IncuCyte) for cell proliferation growth curves. Long-term growth and survival were assessed by colony formation assay. Cell migration and invasion were measured by scratch wound healing and by trans well migration through Matrigel assays, respectively.

Results: Androgen independent PCa cells (PC3 and DU145 cells) show marked upregulation of YAP/TAZ-TEAD transcriptional targets as compared to LNCaP cells. Enzalutamide resistant PCaNO1 and PCaNO2 displayed marked upregulation of YAP/TAZ-TEAD transcriptional targets and increased YAP1/TAZ, and TEAD protein levels compared to parental controls. Enzalutamide resistance was also associated with increased PDL1 expression. Treatment of the cells with YAP/TAZ-TEAD inhibitors significantly suppressed growth and proliferation of these cells. Moreover, inhibition of YAP/TAZ-TEAD pathway also decreased colony formation, migration, and invasion. The effects of inhibition of YAP/TAZ-TEAD pathway on PDL1 are in progress.

Conclusion: YAP/TAZ-TEAD inhibitors block *in vitro* tumor cell proliferation and invasiveness of prostate cancer cells, including those resistant to enzalutamide. Collectively, these findings suggest YAP/TAZ–TEAD inhibition as a promising approach for overcoming therapeutic resistance in subsets of therapy resistant prostate cancer patients.