Screens to identify rationale drug combination strategies for advanced prostate cancer

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Background: among individual patients with advanced, metastatic prostate cancer, a wide range of responses are observed to second generation anti-androgens. Many features measurable in patients have been demonstrated to correlate with altered clinical responses, including genomic events (AR amplification), alternatively spliced mRNAs, protein subcellular localization (e.g. nuclear vs cytoplasmic AR-V7), as well as the number of prior lines of systemic therapy. To fully leverage this information, we aim to functionally identify modulators of anti-androgen response. **Methods:** To achieve this, VCaP cells were infected with a whole genome lentiviral library containing 60,000 unique shRNAs to achieve 1 shRNA infected per cell, then passaged in the presence or absence of enzalutamide. Their genomes were subjected to deep sequencing at different time points, to quantify the relative abundance of lentiviral-integrated sequences corresponding to shRNAs, allowing one to infer the effect of each unique shRNA on cellular proliferation under the specified condition. Subtractive analysis between conditions enables housekeeping genes to be eliminated from the analysis, and a focus placed on genes that specifically modulate the proliferation of cells in the presence of anti-androgens. These potential hits were further filtered by genes known to be altered from human tumor profiling data. **Results:** from this anti-androgen screen, we have identified a handful of exciting epigenetic targets that when inhibited, lead to altered proliferative responses of tumor cells. These are currently undergoing validation. **Conclusion:** the epigenetic state of prostate tumor cells likely controls their degree of sensitivity to androgen receptor antagonists. **Implications:** tumor epigenetics may also predict responses to anti-androgen therapy.

Conflict of Interest: none to report.

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