Integrative (epi) genomic analysis predicts response to anti-androgen therapy in prostate cancer

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Background: Resistance to anti-androgen treatment is a central problem in prostate cancer oncology. Since prostate cancer progression and maintenance depend on androgens, androgen-deprivation therapy has been a mainstay of treatment for advanced disease. Even though patients initially respond to androgen deprivation, majority develop resistance and relapse, progressing to castration-resistant disease, which is nearly always metastatic and lethal. Prioritization of patients for anti-androgen administration could provide invaluable survival benefits, especially for patients with advanced malignancy.

Methods: We have developed an integrative genome-wide computational approach to stratify patients into groups with favorable and poor anti-androgen response, prior to therapy administration. Our method utilizes integrative DNA methylation and mRNA expression analysis of patient profiles to identify (epi) genomic markers of therapeutic resistance.

Results: We have uncovered a panel of 5 differentially methylated sites, which affected expression of their harboring genes, and have shown their significant ability to predict primary anti-androgen resistance (hazard ratio=4.6). In fact, this 5 site-gene panel was able to accurately predict response to anti-androgen therapy in multiple independent patient cohorts and was independent of Gleason score, therapy sub-type, and age. We have demonstrated that our method is robust to noise (i.e., increased false positive and false negative rates) and has significant predictive ability, when compared to random models (p=0.01).

Conclusions: We propose that the identified 5 site-gene panel could be utilized to pre-screen patients and prioritize patients who would benefit from anti-androgen therapy and patients at risk of developing resistance. Such discovery holds a long-term objective to improve therapeutic management of prostate cancer and potentially offer personalized therapeutic advice for patients with advanced malignancy.

Conflict of Interest and Funding Acknowledgements: This work has been supported by the PCF Young Investigator Award and Rutgers SHP Dean’s Research grant. No conflict of interest to declare.