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

Sukanya Panja[1], Sheida Hayati[1], Nusrat Epsi[1], James Scott Parrott[2] and Antonina Mitrofanova[1]*

[1]Department of Health Informatics, [2]Department of Interdisciplinary Studies,

Rutgers School of Health Professions,

Rutgers Biomedical and Health Sciences, Newark, NJ

*corresponding author (amitrofa@shp.rutgers.edu)

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.

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