Predictive modeling of response to androgen-deprivation in prostate cancer

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Background: Resistance to androgen-deprivation is a central problem in prostate oncology. Since prostate cancer progression and maintenance depend on androgens, androgen-deprivation therapy (ADT) 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 androgen-deprivation administration could provide invaluable survival benefits, especially for patients with advanced malignancy.

Methods: We have developed an integrative genome-wide computational approach Epi2GenR to uncover Epigenomic and Genomic mechanisms of treatment Resistance and stratify patients into groups with favorable and poor response to androgen-deprivation, prior to therapy administration. Our method utilizes machine learning specifically tailored to identify an association between DNA methylation and mRNA expression, uncovering (epi) genomic markers of ADT resistance.

Results: Our method has uncovered a panel of 5 differentially methylated sites, which can explain changes in expression of their harboring genes: TTC27, STMN1, FOSB, FKBP6, and CSPG5, and have shown their significant ability to predict primary resistance to androgen-deprivation (hazard ratio=4.6). Furthermore, the 5 site-gene panel was able to accurately predict response to ADT across five independent patient cohorts and was independent of disease aggressiveness, tumor grade at diagnosis, age, and commonly utilized prostate cancer prognostic markers. 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 predictions at random ($p=0.01$). Finally, we simulated a situation when a new incoming patient needs to be assigned risk of resistance using leave-one-out cross validation in five independent cohorts and demonstrated that we can predict risk of resistance to ADT with 90% accuracy.

Conclusions: We propose that the identified 5 site-gene panel could be utilized to pre-screen patients to prioritize those who would benefit from ADT and patients at risk of developing resistance, who should be offered alternative treatment regimens. Such discovery has a near-term potential to enhance personalized therapeutic advice for patients with advanced malignancy and improve prostate cancer management at large.

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