Genetic features predictive of response to anti-androgen therapies in aggressive prostate cancer

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Background:
Genetic alterations in lethal, metastatic prostate cancer include the loss of PTEN, translocation of the TMPRSS2 and ERG genes, upregulation of the androgen receptor (AR), and disruption of the DNA homologous repair pathway driven by mutations to BRCA1, BRCA2, and ATM. Many of these mutations can be observed while the cancer is still localized in the prostate. Here, we seek to identify potential drivers of cancer cell progression and resistance to therapy in situ to inform clinical practice.

Methods:
Using patient tissue from an ongoing neoadjuvant anti-androgen clinical trial at the NCI (NCT02430480), we are examining the cellular features that would predict either exceptional or poor response to anti-androgen therapy. Each patient presents with multiple tumor foci, allowing us to investigate the intratumoral heterogeneity across multiple tumor foci within single patients, as well as investigating the tumor profiles across multiple patients. Some patients have performed remarkably well with residual tumor burdens less than 0.5cc, while others have substantial treatment-resistant cancers. Guided by histopathological analyses, we perform laser capture microdissection on pre-treatment biopsies and spatially matched post-treatment radical prostatectomy to isolate ultrapure tumor foci from each patient. DNA from these foci is used for whole exome sequencing, as somatic copy number alterations and mutations also confirm their evolutionary relationship. This enables us to classify baseline specimens as responder or nonresponder, and we are developing two multiplex panels of twelve markers to characterize these baseline foci.

Results:
In cases analyzed to date, focal PTEN loss has been observed in all nonresponders. Focal ERG staining is absent in 100% of responders and present in 60% of nonresponders. Positive synaptophysin staining is rare at baseline but predicts resistance to treatment with 100% sensitivity. Together, these data suggest that a panel of in situ immunostains assessing oncogene and tumor suppressor alterations can predict resistance to anti-androgen therapy, such that maintaining intact PTEN and lack of aberrant synaptophysin expression predicts response to AR-targeted therapy. The cell biological implications of these data on other endocrine cancers remains of interest for future studies.

Conclusions:
These findings demonstrate the feasibility in identifying intratumoral heterogeneity based on prostate biomarker status both in pre-treatment and post-treatment specimens. Using these data, comprehensive molecular analysis of prostate cancer at diagnosis may better-enable physicians to predict response to anti-androgen therapy and provide tailored treatment based on gene expression status.

Conflicts of Interest:
The authors declare no conflicts of interest.

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