Impact of distinct tumor lineage models on prostate cancer prognosis

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Background

Molecular characterization of prostate cancer (PCa) has revealed several subclasses based on underlying genomic alterations. Understanding the role of these molecular subclasses on prostate cancer progression remains elusive.

Methods

Here we hypothesized that two distinct tumor lineage models of PCa progression involved *ERG|PTEN* and *SPOP|CHD1*, with PTEN and CHD1 deletions as markers of subtype-specific progression events, respectively. To test our hypothesis, we developed two SCaPT (SubClass Predictor Based on Transcriptional Data) models to classify progression events of *PTEN* and *CHD1* deletions purely from transcription data with high confidence. We then classified molecular subclasses from retrospective and prospective cohorts of 8,158 patients via SCaPT models and decision tree.

Results

We found transcriptional alterations pointed to both shared and lineage specific signaling pathways between two tumor lineage models. After classifying molecular subclasses from Decipher cohort, we found progression events of *PTEN* and *CHD1* deletions showed worse prognostic outcomes, when compared to early events of *ERG* fusion and *SPOP* mutation, consistent with our model of lineage-specific tumor progression. Strikingly, the association between *PTEN* deletion and adverse pathologic features at radical prostatectomy, e.g. higher Gleason score, extracapsular extension, seminal vesicle invasion, lymph node invasion, and T3 or T4 cancer stages, was significantly different in the case of *CHD1* deletion, where only high Gleason score was associated to this molecular event.

Conclusions

These findings suggest a paradigm in which specific subtypes of prostate cancer follow distinct lineage models of progression, at both the molecular and clinical levels. Therefore, the interpretation of common risk stratification parameters such as TNM staging may be influenced by the underlying distinct tumor lineages models and molecular subclasses of prostate cancer.

Conflict of Interest

Yang Liu
Employment: GenomeDx
Elai Davicioni
Employment: GenomeDx; Leadership: GenomeDx; Stock and Other Ownership Interests: GenomeDx; Patents, Royalties, Other Intellectual Property: Cancer diagnostics using biomarkers 20140066323; Travel, Accommodations, Expenses: GenomeDx.
Christopher E. Barbieri
Patents, Royalties, Other Intellectual Property: Coinventor on a patent application filed regarding SPOP mutations in prostate cancer by Weill Cornell Medicine.

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