Tumor subtype defines distinct pathways of molecular and clinical progression in primary prostate cancer

Abstract:
We explore the molecular and clinical progression of different genomic subtypes of PCa using distinct tumor lineage models based on human genomic and transcriptomic data. We develop novel transcriptional classifiers, and define “early” and “late” categories of molecular subclasses from 8,158 PCa patients. Molecular subclasses are correlated with clinical outcomes and pathologic characteristics using Kaplan-Meier and logistic regression analyses.

We identify PTEN and CHD1 alterations as subtype-specific late progression events specifically in ERG+ and SPOP mutant tumors respectively, and two distinct progression models consisting of ERG/PTEN and SPOP/CHD1 with shared early tumorigenesis but distinct pathways towards progression. We find that within ERG+ and SPOP mutant subtypes, late events are associated with worse prognosis. Importantly, the clinical and pathologic features associated with distinct late events at radical prostatectomy are strikingly different, PTEN deletions are associated with increased locoregional stage, while CHD1 deletions are only associated with increased grade, despite equivalent metastatic potential.

These findings suggest a paradigm in which specific subtypes of prostate cancer follow distinct pathways of progression, at both the molecular and clinical levels. Therefore, the interpretation of common clinical parameters such as locoregional tumor stage may be influenced by the underlying tumor lineage, and potentially influence management decisions.

Introduction
Background/rationale
Prostate cancer (PCa) is a clinically and molecularly heterogeneous disease. Emerging next-generation DNA and RNA sequencing data point toward different molecular subclasses of prostate cancer, defined by underlying genomic alterations. However, how these early alterations influence subsequent molecular events and the course of the disease over its long natural history remains unclear. We previously established a framework using RNA-based model to classify tumor subtype from transcriptional data, allowing the interrogation of cohorts with the long follow-up necessary to define clinical outcomes.

Objectives
To understand molecular and clinical progression in ERG+ and SPOP mutant subtypes of PCa.

Methods
Study design
We established distinct tumor lineage models of PCa progression, by defining early and late progression events within specific subtypes, and investigating their unique and shared transcriptional alterations and signaling pathways. We developed transcriptional classifiers to categorize subtype-specific early and late states, and applied these to a retrospective cohort including 1,626 patient samples and a prospective cohort including 6,532 samples using microarray-based gene expression data from a clinically available prognostic assay.

Setting
NA

Participants
NA

Variables
Patient outcomes including biochemical recurrence (BCR), metastasis (MET) and prostate cancer specific mortality (PCSM), and clinical variables, including age, race, preoperative PSA, Gleason score, lymph node invasion (LNI), surgical margin status (SMS), extracapsular extension (ECE), and seminal vesicle invasion (SVI)
<table>
<thead>
<tr>
<th>Data sources/ measurement</th>
<th>8*</th>
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<tbody>
<tr>
<td>Bias</td>
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<tr>
<td>Study size</td>
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<td>Retrospective (n=1,626) and prospective (n=6,532) cohorts were derived from the Decipher GRID registry (NCT02609269).</td>
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<tr>
<td>Quantitative variables</td>
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| Statistical methods       | 12 | Kaplan-Meier and logistic regression analyses
                          |    | Logistic regression analyses
                          |    | NA
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**Results**

<table>
<thead>
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<th>Participants</th>
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| Descriptive data | 14* | NA
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<tr>
<th>Outcome data</th>
<th>15*</th>
<th>Retrospective (n=1,626) and prospective (n=6,532) cohorts</th>
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</table>
Main results 16 We found worse metastasis (MET) free survival in both CHD1del and PTENdel tumors compared to the early state within each subtype (SPOPmut and PTENgw). Of note, “early” states of each subtype had similar favorable prognosis, while both “late” states showed similar unfavorable prognosis. Endpoints of biochemical recurrence (BCR) free survival and prostate cancer specific mortality (PCSM) free survival rates followed similar patterns, consistent with previous findings. We found tumors with predicted PTEN deletion were more likely to harbor adverse pathological features at radical prostatectomy: lymph node invasion, extracapsular extension, seminal vesicle invasion, and higher Gleason score in both retrospective and prospective cohorts, consistent with pathologic features of late progression events. Strikingly, however, tumors with predicted CHD1 deletion were only associated with higher Gleason score but no other adverse clinical features.

Other analyses 17 We found specific subtypes of PCa are associated with subsequent molecular changes; tumors with ERG fusions later may acquire PTEN deletions, while SPOP mutant tumors may progress with CHD1 deletion. By comparing the transcriptional pathways between these two tumor lineages, we identified similar enriched functions from the “normal” to “early” states, but divergent signatures from the “early” to “late” states, in multiple localized prostate cancer cohorts. These analyses credential two distinct transcription-based tumor lineage progression models consisting of ERG/PTEN and SPOP/CHD1, with shared early tumorigenesis but distinct pathways towards progression.

Discussion

Key results 18 We identify PTEN and CHD1 alterations as subtype-specific late progression events specifically in ERG+ and SPOP mutant tumors respectively, and two distinct progression models consisting of ERG/PTEN and SPOP/CHD1 with shared early tumorigenesis but distinct pathways towards progression. We find that within ERG+ and SPOP mutant subtypes, late events are associated with worse prognosis. Importantly, the clinical and pathologic features associated with distinct late events at radical prostatectomy are strikingly different, PTEN deletions are associated with increased locoregional stage, while CHD1 deletions are only associated with increased grade, despite equivalent metastatic potential.

Limitations 19 Current genomic and clinical data are derived from bulk tumor sample and limited by intratumor heterogeneity. Molecular and clinical progression for distinct subtypes need to be further investigated at the single cell level.

Interpretation 20 In conclusion, we established mutually exclusive tumor lineage models of PCa progression: ERG/PTEN and SPOP/CHD1. Using transcriptional classifiers to categorize progressive events, we predict lineage and progression status from a large population of human patients, and find that molecularly defined late progression events are associated with worse clinical outcome, but may be associated with distinct clinical pathways toward metastasis. More broadly, these data suggest a paradigm in which specific subtypes of prostate cancer follow distinct molecular pathways of tumor progression, and the interpretation of common risk stratification parameters such as locoregional tumor staging may be influenced by the underlying tumor lineage and degree of molecular progression.

Generalisability 21 Whether tumor lineages and molecular subclasses will add clinical value to current risk stratification tools remains unclear, and need to be prospectively tested in future clinical studies. However, these data do provide compelling rationale to consider molecular subclass in future clinical trial designs.

Other information

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*Give information separately for exposed and unexposed groups.