Integrated classification of prostate cancer reveals a novel luminal subtype with poor outcome.


Abstract

Prostate cancer (PC) is a biologically heterogeneous disease with variable molecular alterations underlying cancer initiation and progression. Despite recent advances in understanding PC heterogeneity, better methods for classification of PC are still needed to improve prognostic accuracy and therapeutic outcomes. In this study we computationally assembled a large virtual cohort (n=1,321) of human PC transcriptome profiles from 38 distinct cohorts and, using pathway activation signatures of known relevance to PC, developed a novel classification system consisting of 3 distinct subtypes (named PCS1 to 3). We validated this subtyping scheme in 10 independent patient cohorts and 19 laboratory models of PC, including cell lines and genetically engineered mouse models. Analysis of subtype-specific gene expression patterns in independent datasets derived from luminal and basal cell models provides evidence that PCS1 and PCS2 tumors reflect luminal subtypes, while PCS3 represents a basal subtype. We show that PCS1 tumors progress more rapidly to metastatic disease in comparison to PCS2 or PCS3, including PCS1 tumors of low Gleason grade. To apply this finding clinically, we developed a 37-gene panel that accurately assigns individual tumors to one of the 3 PCS subtypes. This panel was also applied to circulating tumor cells (CTCs) and provided evidence that PCS1 CTCs may reflect enzalutamide resistance. In summary, PCS subtyping may improve accuracy in predicting the likelihood of clinical progression and permit treatment stratification at early and late disease stages.

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