

A transcription factor activity profile as a prognostic signature for androgen deprivation therapy resistance predisposition in prostate cancer patients

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Introduction & Objectives: Prostate cancer (PCa) is the most common tumor diagnosed in men and is characterized by a diffuse heterogeneity and a marked tendency to develop resistance to standard therapies. The progression of the disease follows the development of resistances to specific treatments such as androgen deprivation therapy (ADT), leading to the onset of the more aggressive, and still untreatable, castration resistant prostate cancer (CRPC). Despite the high number of studies involved in biomarker discovery for the prediction of ADT resistance predisposition, several obstacles remain in the implementation of the identified signatures. Low reproducibility across laboratories, differences in experimental platforms and techniques, the inherent heterogeneity of PCa and insignificant clinical utility or small gains in sensitivity and specificity beyond PSA, hampers the identification, validation, and implementation of biomarkers signatures¹. By considering the functional interactions among genes and relying less on minor variations due to different platforms and protocols adopted, a pathway-based analysis is more likely to provide more consistent results across different data sets.

Materials & Methods: We performed the enrichment of a set of transcription factors (TF) regulons, namely sets of TF-targets relationships, identified from a dataset of 18 PCa xenograft to reveal per-sample lists of active TFs in 3 independent patient cohorts.

The three datasets used for validation are composed of RNAseq data obtained from fresh-frozen tissue specimens and survival timing for each patient. In greater detail:

- 27 local and hormone naïve tumors (Tampere University Hospital) of which 15 progressed into CRPC within 7 years of follow-up;
- 49 radical prostatectomies (Erasmus Medical Center, Rotterdam) of patients who experienced a biochemical recurrence after surgery (n=23) or not (n=26);
- 497 primary tumors (TCGA) of which 93 experienced a biochemical recurrence.

A permutation analysis has been performed on each RNAseq profile to evaluate the enrichment status of 1308 regulons identified from the preclinical models. Cox regression analysis has been adopted to assess the ability of the agreement with prostate specific TF-targets relationships to predict progression free time. The same survival analysis has been repeated by using a gene signature to stratify patients in high and low risk groups as suggested by an independent research team ²

Results: The information stored into regulons enrichment scores showed better performances in discriminating progressive from non-progressive tumors in the 3 validation cohorts investigated. The prognostic value of the regulons identified from orthograft data, confirms the utility of PCa preclinical models for biomarker discovery.

Conclusions: A predictive model based on TF activity profile is more robust than gene expression signatures in classifying tumors predisposed to recurrence and, at the same time, provides a better understanding of the mechanisms underlying disease progression.

Differentially Expressed Genes and Signature Pathways of Human Prostate Cancer, Mayers et al – 2015

A TMEFF2-regulated cell cycle derived gene signature is prognostic of recurrence risk in prostate cancer, Georgescu et al - 2019