Integrative tissue "omics" reveals a biomarker gene signature that re-defines prostate cancer risk for Gleason Score 6 & 7

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Background: It is well known that prostate cancer (PCa) is a progressive disease involving multiple gene alterations. Gleason score (GS) is a morphologic feature of PCa used to evaluate the risk of disease progression. However, GS often fails to clearly distinguish between indolent and aggressive disease in low-intermediate GS. The aim of this study was to identify potential additional biomarkers for PCa risk stratification.

Methods: An in-depth proteomics analysis (LC ESI-MS/MS) was performed on human PCa and BPH tissues. First, we identified differentially expressed proteins between PCa and BPH samples. We then filtered the proteins based on peptide spectrum matches and selected a panel of candidates. To assess and validate the clinical significance of these peptides we performed an integrative bioinformatics analysis using public database repositories.

Results: Here, we found 14-3-3ζ/δ, an androgen receptor downstream target, as one of the proteins enriched in PCa compared with BPH. We identified high expression of 14-3-3ζ/δ to be strongly associated with poor prognosis across different PCa datasets (HR=3.07, P<0.001 [GSE16560]; HR=3.94, P<0.001 [GSE70769]). Further, multivariate analyses displayed high significant correlation with poor prognosis, independent from GS, age, PSA at diagnosis and TMPRSS2-ERG fusion (HR=2.21, P<0.001 [GSE16560]; HR=2.32, P=0.01 [GSE70769]). Next, we focused on the expression of *YWHAZ* (14-3-3ζ/δ encoding gene) in men with GS 7 to identify its potentiality as a predictor of unfavorable outcome. Results show that high expression of *YWHAZ* in the GS 7 (3+4) and (4+3) subgroups significantly correlated with decreased overall survival (HR=2.04, P=0.027 and HR=2.32, P=0.05, respectively). Further we re-screened the enriched PCa genes for GS 6-7 (3+4) and found a potential biomarker gene signature for risk stratification in low-intermediate GS. Patients with co-occurrent gene dysregulation for GDF15, APOE, NDRG1 and YWHAZ were significantly associated with poor clinical outcome (overall survival HR=1.6, P<0.05 [GSE16560]; or relapse free survival HR= 2.1, P<0.05 [GSE70769]).

Conclusion: In summary, this increased gene signature appears to be critical for overall or relapse free survival in low-intermediate GS patients. Moreover, 14-3-3ζ/δ rises as a promising prognostic biomarker in PCa, independent from GS, especially aiding in disease risk stratification for GS 6-7.

Conflict of Interest: None

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