A genomic fingerprint for detecting small cell prostate cancer in metastatic and localized disease

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BACKGROUND: Prostatic small cell carcinoma (SCC) is a rare aggressive prostate cancer variant that is molecularly, histologically, and clinically distinct from the differentiated adenocarcinoma type. The emergence of the SCC occurs mostly in patients with high-grade adenocarcinoma who fail androgen deprivation treatment (ADT). Identifying localized primary tumors with SCC-like genomic profile is of paramount clinical importance for these patients.

METHODS: In this work we characterized the genomic fingerprint of de-novo prostatic SCC using Decipher® prostate cancer classifier assay and developed a genomic model to identify primary prostatic adenocarcinoma with SCC-like genomic fingerprint.

RESULTS: We first generated whole transcriptome expression profiles of prostatic FFPE tissues from 11 histologically selected *de novo* SCCs and 12 treatment-naïve high grade (Gleason 9-10) adenocarcinomas. We hypothesized that comparing these histologically 'pure' forms of disease could circumvent some of the challenges posed by the molecular heterogeneity inherent in heavily treated tissue. A SCC genomic fingerprint (SCGFt) of 28 genes involved in NE differentiation, cell proliferation, AR-signaling and RB loss was discovered. As a first test of the SCGFt we applied it to an expanded version of our original discovery cohort including additional 14 foci from patients with mixed histology tumors where we either sampled predominant adenocarcinoma (termed mixed-Adeno) or SCC (mixed-SCC) components. Hierarchical clustering using the SCGFt demonstrated that 4/7 SCC-mixed foci were transcriptomically very similar to SCC, while the remaining three had profiles more reminisce of adenocarcinoma. Across three independent CRPC/mCRPC cohorts (n=338), SCC specimens generally grouped together under the influence of the SCGFt, although there were some outliers. The SCGFt was translated into SCC genomic score (SCGS) using logistic regression model. In retrospective cohorts, patients with high SCGS developed metastatic outcome and failed adjuvant ADT suggesting SCGS may act as a predictive biomarker. SCGS was measured in a cohort of 2,293 prospective patients from the Decipher GRID and approximately 2% of patients showed to have SCC-like genomic profile with higher risk of developing metastasis based on the Decipher test. These 2% showed higher NE biomarker expression, lower AR-output activity and high cell cycle activity.

CONCLUSIONS: Approximately 2% of localized PCa harbor a SCC-like genomic fingerprint with low AR-signaling and high NE biomarkers and potential ADT resistance. This may help guide subsequent management and provide additional potential therapeutic targets.

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