Gene Expression Meta-Signature of Neuroendocrine Prostate Cancer

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BACKGROUND: Neuroendocrine prostate cancer (NEPC) is rare historically but may be increasing in prevalence as patients potentially develop resistance to contemporary anti-androgen treatment through a neuroendocrine phenotype. Diagnosis can be straightforward when classic morphological features are accompanied by a prototypical immunohistochemistry profile, however there is increasing recognition of disease heterogeneity and hybrid phenotypes. In the primary setting, small cell prostatic carcinoma (SCPC) is frequently admixed with adenocarcinomas that may be clonally related, while a small fraction of SCPC's express markers typical of prostatic adenocarcinoma. Gene expression patterns may eventually help elucidate the biology underlying equivocal cases with discordant IHC, however studies to date have focused on prototypical cases and been based on few patients due to disease rarity.

METHODS: We used gene signatures to evaluate NEPC datasets and catalog unusual samples. We then developed a meta-signature and model through outlier analysis of NEPC tumors from 15 patients across 6 frozen tissue microarray datasets, and applied this model to 16 primary SCPC's and 16 primary high grade adenocarcinomas profiled on exon arrays from archived formalin-fixed paraffin-embedded (FFPE) material. We finally developed a nearest-centroid-classifier for 3 categories of primary tumors (prototypical SCPC, atypical SCPC, and prototypical adenocarcinoma) using differential expression analysis for feature selection.

RESULTS: We identified 69 genes with consistent outlier expression in at least 80% of NEPC patients from meta-analysis datasets, and found similar behavior of NEPC and small cell lung cancer with respect to these genes. A 3-centroid-classifier (trained on 9 primary SCPC, 9 primary adenocarcinomas, and 4 primary atypical SCPC) achieved a 4.5% error rate based on leave-one-out-cross-validation (LOOCV). The classifier predicted SCPC-features in 40% (2/5) of known mixed adenocarcinomas, 0.6% (2/355) of high-risk adenocarcinomas from a retrospective radical prostatectomy (RP) cohort in which both predicted cases developed metastases, and 0.3% (4/2293) of adenocarcinomas from a prospective RP cohort.

CONCLUSIONS: Meta-analysis of expression data from multiple prototypical NEPC datasets generates a robust model of NEPC. FFPE material may be used to develop a model of prototypical and atypical SCPC in the primary setting, with potential prognostic implications.

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