Luminal and basal subtyping of prostate cancer is prognostic and predicts response to androgen deprivation therapy

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Abstract

Background: There is a clear need to develop a molecular subtyping approach for prostate cancer which can identify clinically distinct subgroups that benefit from specific therapies. Our goal was to subtype prostate cancer based on luminal versus basal lineage and predict clinical outcomes and treatment response.

Methods: We apply the PAM50 classifier to subtype 3,782 retrospectively (median follow-up 10-years) and prospectively collected prostate cancer samples into luminal- and basal-like subtypes using a high-density microarray platform run in a CLIA-certified laboratory. Samples were obtained from multiple academic institutions including the Mayo Clinic, Cleveland Clinic, Johns Hopkins University, Thomas Jefferson University, and the Durham VA as well as commercial clinical samples from Decipher GRID™.

Results: We demonstrate that PAM50 segregates prostate cancer into three reproducible subtypes in both retrospective cohorts and on prospective validation: luminal A (33.3%-34.3%), luminal B (28.5%-32.6%), and basal (34.1%-37.1%). Luminal B prostate cancers exhibited the worst clinical prognoses, followed by basal and luminal A subtypes (10-year biochemical recurrence-free survival: 29/39/41%; distant metastasis-free survival: 53/73/73%; prostate cancer-specific survival: 78/86/89%; overall survival: 69/80/82% respectively) on both univariable and multivariable analyses accounting for standard clinicopathologic prognostic factors. Known luminal lineage markers, such as NKX3.1 and KRT18, and the basal lineage CD49f signature, were enriched in luminal- and basal-like cancers respectively, demonstrating the connection between these subtypes and established prostate cancer biology. While both luminal-like subtypes were associated with increased AR expression and signaling, only luminal B prostate cancers were significantly associated with post-operative response to androgen deprivation therapy (ADT) in a subset analysis matching patients based on clinicopathologic variables (interaction p=0.006, luminal B 10-year metastasis: 33% (treated) vs. 55% (untreated), non-luminal B: 37% (treated) vs. 21% (untreated)).

Conclusions: Luminal- and basal-like prostate cancers demonstrate divergent clinical behavior, and luminal B patients respond better to post-operative ADT than non-luminal B patients. These findings contribute novel insight into the biology of prostate cancer, and provide the first predictive clinical tool for personalizing the treatment of prostate cancer.

Conflicts of Interest:
MRC has honoraria from Takeda, consulted for Myriad, Astellas, Dendreon, Janssen, has research funding from Genomic Health, Myriad, GenomeDx. CS has a patent: Compositions and methods for the analysis of radiosensitivity, in the process of being licensed to PFS Genomics, and an ownership interest in PFS Genomics. AER has consulted for GenomeDx, has an ownership interest in GenomeDx, and research funding from MERCK, Novartis, Metamark. PLN has consulted for Medivation, GenomeDx, Ferring, Nanobiotix. EAK has consulted for Berg, speakers' bureau for Genomic Health, and research funding for GenomeDx, Genomic Health. RJK has research funding and travel expenses from GenomeDx. EMS has consulted for GenomeDx, Myriad Genetics. ED is an employee, leadership, and has ownership in GenomeDx, and has a patent: Cancer diagnostics using biomarkers. PRC has honoraria from Takeda Pharmaceutical, Genomic Health, and consulted for Janssen Pharmaceutical, Medivation. AMC is on the advisory board for Wafergen, ThermoFisher and has patents on SChLAP1, licensed to GenomeDx and long-noncoding RNAs. SAT has honoraria from Ventana Medical Systems, consulted for Ventana Medical Systems, Astellas/Medivation, Janssen, has research funding from Thermo Fisher Scientific, travel expenses from Thermo Fisher Scientific, patents on ETS gene fusions in prostate cancer, the diagnostic field of use has been licensed to Hologic/Gen-Probe Inc., who has sublicensed some rights to Ventana Medical Systems/Roche. FYF has leadership, ownership in PFS Genomics, consulted for Medivation/Astellas, GenomeDx, Celgene, Varian Medical Systems, has patents: Compositions and methods for the analysis of radiosensitivity, in the process of being licensed to PFS Genomics, and Long-noncoding RNAs. MA and JL are employees of GenomeDx. NE has a patent: Cancer diagnostics using biomarkers and is an employee at GenomeDx. SGZ has travel expenses from GenomeDx and a patent: Compositions and methods for the analysis of radiosensitivity, in the process of being licensed to PFS Genomics. SLC is an employee of PFS Genomics. RBJ has a patent: Cancer diagnostics using biomarkers. PB has served on advisory boards for Novartis, AbbVie, Astellas, Janssen,

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