Defining the molecular phenotypes of metastatic castration-resistant prostate cancer and their sensitivity to FGF pathway inhibition

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Background: Widespread and long-term use of androgen deprivation therapy (ADT) is changing the molecular and phenotypic landscapes of prostate cancer. Observations made through our longstanding rapid autopsy and patient derived xenograft (PDX) programs at the University of Washington support a shift in metastatic castration-resistant prostate cancer (mCRPC) towards androgen receptor (AR)-null phenotypes, such as neuroendocrine (NEPC) and double negative (DNPC). Currently, there are no effective therapies for AR-null mCRPC. We showed previously that DNPC (AR-null, NE-null) bypasses AR-dependence through fibroblast growth factor (FGF) signaling. However, the role of the FGF pathway in other molecular mCRPC subtypes remains to be determined.

Methods: Molecular characterization of mCRPC specimens and LuCaP PDX models was conducted through immunohistochemistry, RNA sequencing and gene-set enrichment analysis. RE1-silencing transcription factor (REST) function was examined using siRNA-mediated knockdown in AR+ and AR- cell lines. Multiple LuCaP PDX lines were used to examine responses to CH5183284 (FGFR inhibitor) alone or in combination with enzalutamide (AR-expressing models only).

Results: We define five mCRPC subtypes that are categorized by the presence or absence of AR or neuroendocrine (NE) transcriptomic signatures: (i) adenocarcinoma (AR+/NE-), (ii) AR-Low (low AR expression with concomitant decreases in AR regulated genes), (iii) amphicrine (tumor cells co-expressing AR and NE markers, AR+/NE+), (iv) DNPC (AR-/NE-) and (v) NEPC (AR-/NE+). Immunohistochemistry of mCRPC and PDX models for AR, prostate specific antigen, synaptophysin, chromogranin A, and other clinically relevant markers reflected the AR/NE transcriptomic signature. Thus, we propose a clinically relevant 26-gene signature to classify mCRPC specimens. Furthermore, we previously showed that loss of REST activity through alternative splicing of REST mRNA may promote the NEPC phenotype. Here, PCR analysis of mCRPC and LuCaP models identified the REST splice variant exclusively in amphicrine and NEPC specimens. However, siRNA-mediated knockdown of REST in AR+ and AR- CRPC cell lines showed that loss of REST activity supports NEPC and amphicrine phenotypes but is not necessarily sufficient for conversion to NEPC. Finally, we conducted preclinical testing of the FGFR inhibitor CH5183284 in multiple PDX models representing the five mCRPC subtypes described above. Interestingly, AR-expressing CRPC PDX models responded to combination CH5183284 and enzalutamide treatment only and NEPC PDX models had line-specific responses to CH5183284 monotherapy.

Conclusions: Our data highlight AR and REST transcriptional programs in maintaining phenotypic stability in mCRPC and explain the phenotypic heterogeneity of mCRPC in the abiraterone/enzalutamide era. Understanding the mCRPC subtypes that depend on the FGF pathway for survival and proliferation will inform treatment and lead to the development of novel therapeutic strategies for advanced disease.

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