A novel metastatic prostate cancer model from an African American man with small-cell characteristics

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Small-cell prostate cancer (SCPC) is a class of prostate cancers that are often associated with rapid disease progression and resistance to standard of care treatment yet have been largely understudied. To obtain mechanistic insights about SCPCs, a patient-derived organoid (PDO) model derived from a lymph node metastasis of an African American man bearing treatment-refractory metastatic SCPC was established and named "Lym-1". The organoid culture of Lym-1 supported robust xenograft tumor growth and metastatic development to bone, adrenal glands and kidney, which is consistent with the metastatic sites detected within the donor patient. Importantly, every tumor developed *in vivo* presented positive IHC staining for neuroendocrine prostate cancer (NEPC) markers including ASCL1, SYP, and SOX2, negative for AR, and exhibited a high fraction of Ki-67 positive cells, a phenomenon frequently observed in SCPCs. Through genomic profiling, bi-allelic losses of *RB1* and *TP53*, both drivers of NEPCs, were confirmed. Copy number profiling also identified an arm-level amplification at 8p in Lym-1, which was frequently deleted in prostate cancers, but copy number gains reported in small-cell lung cancers. Additionally, comparing to various mCRPC tumors and patient-derived models, Lym-1 and its donor disease shared a high degree of transcriptomic similarities with NEPC, SCPC, and particularly transformed SCPC. Interestingly, plasma cfDNA collected from the patient revealed identical genomic alterations, clonal structures and transcriptional activities to those identified in the organoid model. In conclusion, this model, Lym-1, faithfully recapitulates patient metastatic behaviors with NEPC molecular characteristics and supports robust discovery of novel mechanisms that drive disease progression of SCPC with a complex clinical history.

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