Elucidating Drivers of Neuroendocrine Plasticity in Mouse Models of Prostate Cancer

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Abstract: Lineage plasticity is a hallmark of cancer that enables tumor cells to evade therapies and develop resistance. Understanding the molecular drivers of plasticity is crucial for managing treatment resistance in the clinic. We previously established a novel mouse model of the neuroendocrine lineage plasticity in prostate cancer, identifying *Rb1* loss, tumor microenvironment input, and *Ascl1* expression as key factors for the neuroendocrine transition. Using advanced single-cell sequencing and spatial transcriptomics alongside integrative computational methods, we confirm the dynamic nature of this adenocarcinoma-to-neuroendocrine transition, revealing significant transcriptional and epigenetic heterogeneity within tumor populations. This process is characterized by sharp phenotypic shifts at key transition points, with the identification of a rare transitory tumor population bridging these two extremes. Our findings nominate several transcription factors co-expressed with *Ascl1* as potential drivers of the neuroendocrine transition. Lineage tracing with single cell molecular barcoding uncovers a striking polyclonal origin of the neuroendocrine transition, where multiple transition-competent luminal adenocarcinoma clones independently converge upon a plastic cell state. This dynamic state is defined by progressive activation of neuroendocrine programs, sharp induction of AP-1 activity, and engagement of cell-intrinsic inflammatory pathways. These findings shed additional light into co-regulated genetic and transcriptional programs governing therapy resistance and tumor evolution. By pinpointing these critical molecular players, our work opens new avenues for disrupting lineage plasticity, offering promising therapeutic strategies to overcome treatment resistance in prostate cancer.

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Conflicts of Interest Disclosure Statement: C.L.S. served on the Board of Directors of Novartis (2013-2025), is a cofounder of ORIC Pharmaceuticals and is a co-inventor of the prostate cancer drugs enzalutamide and apalutamide, covered by US patents 7,709,517; 8,183,274; 9,126,941; 8,445,507; 8,802,689; and 9,388,159 filed by the University of California. C.L.S. is on the scientific advisory boards for the following biotechnology companies: Beigene, Blueprint Medicines, CellCarta, Column Group, Foghorn, Housey Pharma, Nextech, PMV Pharma and ORIC. D.P. is on the scientific advisory board of Insitro. The other authors declare no competing interests.