

Deconstructing Plasticity: Mapping Determinants of the Neuroendocrine Transition

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Abstract: Lineage plasticity allows cancers to evade therapy by entering cell states that bypass the dependencies of the original tumor, yet how tumor cells escape lineage constraints to access distantly related identities remains unclear. This problem is exemplified in prostate cancer, where treatment resistance can culminate in neuroendocrine prostate cancer (NEPC), an aggressive state distinct from the adenocarcinoma from which it arises. Using temporally resolved mouse models, single-cell and spatial profiling, and molecular lineage tracing, we reconstruct this transition at high resolution. We find that neuroendocrine transformation does not proceed through a gradual continuum but instead occurs through an abrupt, discontinuous leap to a convergent endpoint. This leap is preceded by epigenetic erosion within adenocarcinoma, as tumor cells progressively loosen luminal identity and acquire a broader plasticity program. Rare transitional populations emerge from these states, localize adjacent to nascent neuroendocrine lesions, and traverse evolving routes toward neuroendocrine commitment. Expressed-barcode lineage tracing demonstrates that NEPC descends from luminal adenocarcinoma and arises polyclonally through multiple independent reprogramming events. Spatial transcriptomics further reveals that independent transitional clones converge within multiclonal niches adjacent to NEPC, implicating the local tumor microenvironment in shaping lineage transition. Unexpectedly, Rb1-proficient tumors that never progress to overt NEPC nevertheless harbor rare neuroendocrine-like cells. Thus, the critical barrier to transformation is not access to neuroendocrine identity itself, but the accumulation of transition-competent precursor states that enable efficient and recurrent lineage switching, a property conferred by Rb1 loss. Together, these findings identify genotype-dependent epigenetic erosion as a mechanism that establishes competence for abrupt lineage reprogramming and implicate spatially organized tumor niches in shaping this process.

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