Interrogation of chromatin dynamics of pancreas cancer cell state transitions in 4D

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Abstract**:** Pancreatic ductal adenocarcinoma (PDAC) portends a 5-year survival of 13% and is on track to become the second-most prevalent cause of cancer-related death by 2030. Cancer cell plasticity—the capacity to differentiate and adapt to cell-extrinsic pressure via non-genetic mechanisms—promotes tumor progression and is a major cause of treatment failure. Thus, targeting plasticity in PDAC is a promising therapeutic concept. In preliminary experiments, we found that PDAC cells with basal epithelial identity harbor high plasticity, whereas classical and mesenchymal cell states display a fixed identity. We further uncovered that basal PDAC cells drive tumor maintenance and adaptation to KRAS-targeted therapy. These results cast this cellular subset as an attractive therapeutic target for suppressing PDAC plasticity and drug resistance. We hypothesize that the highly plastic state in PDAC is supported by unique chromatin landscapes and 3D enhancer-promoter connectomes that enable rapid acquisition of either classical or mesenchymal fates. Here, we propose to define the chromatin states and 3D regulatory networks of the basal, classical, and mesenchymal PDAC cells *in vivo* with the goal to identify and perturb central regulatory nodes that dictate cell fate decisions. To incorporate the fourth dimension—time—we will leverage our lineage-tracing systems to investigate chromatin states of cells undergoing active transitions or harboring a memory of a recent transition. This study will provide an unprecedented dynamic understanding of chromatin state changes in pancreas cancer, which may elucidate new therapeutic entry points for targeting plasticity and cell state transitions in PDAC and, potentially, other cancers.