Unmasking Tumor Heterogeneity: SOX9 Regulates EMT in a Novel High-Plasticity Cell State

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Lung cancer is the leading cause of cancer-related mortality. Epithelial-mesenchymal transition (EMT), a process by which epithelial cancer cells acquire a mesenchymal phenotype, reportedly drives chemoresistance and metastasis in lung cancer patients. Therapeutic targeting of EMT is challenging since its mechanisms are poorly understood. A 2020 study applied single-cell RNA sequencing (scRNA-seq) to an in vivo mouse lung adenocarcinoma model and identified a novel High-Plasticity Cell State (HPCS). The HPCS were the only cells to undergo chemotherapy-induced EMT following cisplatin treatment (cEMT) and metastasis-associated EMT in late-stage tumors (mEMT). However, the genes that regulate these transitions are still unknown. The research reported here further analyzes the scRNA-seq data to investigate if the SOX9 transcription factor, which induces EMT of lung cancer cells in vitro, also orchestrates cEMT and mEMT of the HPCS in vivo. To model cEMT and mEMT, epithelial and mesenchymal HPCS cells were ordered in single-cell trajectories across pseudotime. As hypothesized, SOX9 was differentially expressed across pseudotime ($q<0.001$) and was the first gene activated (McFadden's $R^2>0.03$) in both trajectories, suggesting SOX9 is a master regulator of EMT. Correlation-based inference of gene regulation across pseudotime suggested SOX9 upregulates the SNAI2 transcription factor which then initiates cadherin switching (Pearson's $r>0.5$). Ultimately, this study identifies SOX9 as a master regulator of EMT of the novel HPCS, a finding that enables the development of EMT-targeting anticancer therapies. To apply this finding, future research will aim to develop HPCS-specific CRISPR-Cas9 vectors to selectively ablate SOX9 in the HPCS and suppress cEMT and mEMT.

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