# Fate-Seq Reveals Pre-Existing Cell States of Immune-Mediated Resistance in Gastrointestinal Cancer Cells

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Non-genetic resistance allows subsets of cancer cells to evade apoptosis and persist despite therapy. To investigate the non-genetic determinants of immune-mediated cell resistance, we applied Fate-Seq, a single-cell functional genomics approach, to gastrointestinal cancer cell lines. Using a same-cell design, the exact cell monitored by live-cell imaging is subsequently recovered and sequenced, preserving its identity together with detailed dynamic data. For each cell, we extracted time-resolved phenotypic features, including reporter dynamics, cell division, death timing, survival, and morphological changes following exposure to TRAIL, an immune effector. We then analyzed transcriptomic profiles across the cell lines to identify both conserved and cell-line-specific molecular programs associated with the predicted phenotype. This comparative analysis allowed us to characterize differentially ex-pressed genes, enriched pathways, and drug targets to validate. In parallel, we developed a sensitivity-resistance score adapted to each cell line, designed to be projected onto control samples to reveal pre-existing transcriptional states associated with sensitivity or resistance along a continuum. Together, our work provides a framework to connect short-term cellular dynamics, single-cell transcriptomes, and intrinsic variability in immune resistance across gastrointestinal cancer models. It provides a computational framework for identifying predictive molecular signatures of cancer cell fate.