RECONSTRUCTING SINGLE CELL LINEAGE TRAJECTORIES AND DIVERSITY IN FATES DURING THE EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)

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Abstract: Understanding the diverse trajectories and cell fates associated with the epithelial-mesenchymal transition (EMT) remains challenging, especially when it comes to lineage tracing at the single-cell level using single-cell RNA sequencing (scRNAseq) data. In this study, we employed a mathematical inference approach called optimal-transport analysis to infer ancestor distributions and reconstruct the most probable past trajectories of different cell fates during TGF-beta-induced EMT in the MCF10A cell line. Our analysis revealed three distinct temporal processes: those resulting in a low EMT, partial EMT, and high EMT state. The partial EMT trajectory exhibited substantial variations in the EMT signature and displayed unique cellular characteristics, including high stemness, low proliferation scores, and a potent cellular response to hypoxia. Significantly, we observed downregulation of the EED and EZH2 genes along the partial EMT trajectory, alongside the early high expression of TGFBI, KRT8, and CDH1 — a finding that aligns with recent CRISPR-associated knock-out screening studies. Lastly, we have comprehensively examined key early genes associated with proliferation and metabolism across all three EMT fates. Our discovery provides a novel method to identify different EMT subprograms using scRNAseq data and offers a novel repertoire of potential targets for modulating specific EMT trajectories.

Bio: Yu-Chen completed his MD at Taipei Medical University in Taiwan. He pursued further studies in Applied Mathematics at the University of Washington, Seattle, where he earned his PhD under the guidance of Dr. Hong Qian. Yu-Chen focused on the theory of random perturbations of dynamical systems and statistical ensemble theory, exploring applications in biology and biophysics. He earned The Boeing Fellowship and the Boeing Outstanding Research Award. Currently, Yu-Chen's postdoctoral research at Harvard University revolves around applying the principles of dynamical systems and stochastic processes to advance cancer modeling research.