

Coupling between cell cycle and cell fate change

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Dynamical systems theory has long been utilized to describe cellular processes; however, the main challenge is the lack of quantitative information for constraining models. Combining our recently developed approaches of single cell genomics data analyses and live cell imaging studies within the framework of dynamical systems theory, we investigated how epithelial-to-mesenchymal transition (EMT) couples to cell cycle progression. Analysis of scRNA-seq data predicts two parallel paths corresponding to G1/S and G2/M arrest, and we are testing this through live cell imaging studies with A549/Vim-RFP/PCNA-eGFP cell lines.

Keywords — dynamical manifold, bifurcation, attractor, vector field.

I. BACKGROUND

DYNAMICAL systems theory-based modeling is a fundamental tool in quantitative biology. Analyses of simple network motifs have revealed important ‘design principles’ in biological networks. Such simple networks are embedded in a much larger densely-connected network with a broad range of time scales, and a focused area is to study the coupling between different cellular processes. However, quantitative studies beyond simple networks, face a technical **dilemma**; existing high throughput single cell techniques are destructive and cannot provide true long-time dynamical information, while fluorescent-based live cell imaging techniques are intrinsically limited to a small number of channels and are challenging for long-time imaging due to cytotoxicity concerns. In recent years my lab has tackled this grand challenge by analyzing fixed- and live-cell data within the framework of dynamical systems theory¹⁻⁴.

Epithelial-to-mesenchymal transition (EMT) and the reverse process, mesenchymal-to-epithelial transition (MET), play important roles in embryonic development, tissue regeneration, and pathological processes such as cancer metastasis and fibrosis. Previous reports suggest that cells

undergo G1/S and/or G2/M cell cycle arrest while undergoing EMT. It is unclear how the EMT and cell cycle programs couple to each other and regulate the cell fate transition process⁵. Mechanistic understanding of the coupling has both an important basic science and biomedical significance.

II. RESULTS

We acquired scRNA-seq data for human MCF10A cells treated with various doses of TGF- β . Then we reconstructed the genomewide vector fields for each TGF- β concentration. The vector fields reveals that epithelial attractors are destabilized with increasing TGF- β concentration. In addition, least-action path analysis revealed two groups of trajectories, consistent with our previous live-cell imaging studies using A549 cells^{3,4}. Through in silico perturbations we identified top-ranked genes that regulate the core EMT-cell cycle network.

Note that a direct usage of dimensionality reduction approaches may distort the topological structure of the dynamical manifold of a cellular system, we adopted a procedure that divides the state space into cell cycle-dependent- and -independent subspaces and then dimensionality reduction was performed. We reconstructed a torus-shaped manifold for the EMT process. We analyzed several other scRNA-seq EMT data and observed similar dynamical behaviors.

Next, we generated an A549/Vim-RFP/PCNA-eGFP cell line, and we are performing live cell imaging studies to test our model predictions.

III. CONCLUSION

Our results support that EMT can proceed through either G1/S arrest or G2/M arrest. We hope to provide mechanistic understanding how a cell makes the decision between EMT and cell cycle progression.

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Acknowledgements: This work was funded by NIH grant R37 CA232209 and R01DK119232.

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