Gene regulatory network model of Pancreatic cell differentiation and reprogramming

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***Short Abstract* — It is generally believed that various cell types are different attractors of the gene regulatory network. The development of a multicellular organism is corresponding to the trajectory moving from one attractor to various attractors in the gene landscape. However, it is still unknown how the multi-stabilities are constructed, and what's the driving force of cell differentiation and cell reprogramming. Here we take the development of the pancreatic cell as an example to explain theses molecular mechanism underneath. The gene regulatory network of pancreatic cells are reconstructed from the experimental data of regulation relationship among transcription factors and gene expression profile. A mathematical model of coupled gene switches is developed to reproduce the key gene expression profile and knock-out experiments. Two different gene switch mechanisms are identified to explain the differentiation of pancreas cells. We also discuss the counter-intuitive role of gene Pdx1 in cell reprogramming and derive testable predictions to produce new reprogramming recipes.**

***Keywords* — Gene regulatory network, pancreatic cell, cell differentiation, cell reprogramming, mathematical modeling**

I. Introduction

THIS study has been inspired by the successful reprogramming of terminally differentiated exocrine cells of the pancreas in mice to insulin-producing cells with all characteristics of pancreatic β-cells [1]. Even it is done successfully in experiment, the molecular mechanism of cell reprogramming and cell differentiation in general is yet unknown. The reprogramming recipe more or less comes from the trial and error. There is no sound guide line how to design a working reprogramming recipe.

Cell differentiation is the result of dynamical interactions between signaling pathways and gene regulatory networks. . For generic cases, assumed dynamical interactions have been translated into mathematical equations, the analysis and simulation of which provided a solid qualitative understanding of cell differentiation [2,3,5,7]. Quantitatively, the early stages of sea urchin development have been successfully modeled[4].

Here we apply this established modeling concept to build a mathematical model of pancreatic cell differentiation and then analyze it to propose some optimized reprogramming gene recipes.

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II. Results

We propose that the multi-stabilities of a gene regulatory networks can be constructed from a hierarchy of cross-inhibiting gene switches. The cell differentiation is initiated by the signals to change the genetic landscape, and then is driven by the noise to commit to the certain cell linage afterwards.

A. Developmental differentiation

Nine genes have been identified as essential for β-cell differentiation [1]. We group these nine into six groups. Each corresponds to a single variable in our model.

Our model of pancreatic differentiation reproduces the gene expression patterns of each cell type, and the gene expression profile during the pancreatic cell development.

B. Knock-out mutants

Four different simulations with a single marker gene held at zero reproduce the absence of β-cell differentiation under these mutant conditions.

C. Cell Reprogramming

We show that our model which was developed to reproduce pancreas development in wild type and mutant conditions also correctly reproduces the reprogramming experiments.

III. Conclusion

We have developed a model of pancreatic cell differentiation that reproduces developmental and reprogramming data as well as predicts optimized strategies for reprogramming.

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