Design principles of the regulatory module in hematopoietic differentiation network

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***Short Abstract* —Regulatory mechanisms that control the mixed lineage gene expression patterns to specify cell fate have largely remained unexplored due to the complexity of the regulatory networks. Recently a recursively wired transcription factor module has been identified in the hematopoietic stem cell differentiation network. The module is a fully connected triad comprised of multiple positive feedback loops. Similar modules in other stem cell networks suggest that the module is a recurrent motif with a unique function. We use a computational approach to gain insight into the specific function of this module.**

I. Introduction

Hematopoietic Stem Cells (HSCs) give rise to a variety of functionally different cell types [1]. During differentiation, daughter cells derived from HSCs undertake a series of commitment decisions, becoming progressively more restricted in their lineage potential, until eventually lineage-committed end stage cells are generated [2]. The ability of HSCs to contribute to different hematopoietic cell lineages is governed by the interplay of many different transcription factors in the differentiation Gene Regulatory Network (GRN) [3]. Recent work by the Gottgens group has identified a triad module of multiple positive feedback loops consisting of Scl, Gata2 and Fli1 that has been shown to play an important role in the HSC lineage selection process [3]. The existence of similar modules in other stem cells indicates the significance of this GRN module architecture.

Using experimental results from the Gottgens group, we constructed a mathematical model to investigate the dynamic behavior of the HSC triad module. Our analysis revealed the inherent multistability of the triad module and highlighted how the module plays a role in initiating irreversible gene expression programs for differentiation in response to extracellular signals. Our results also provide important conclusions about the design of the module and module interactions.

II. Model

The Scl, Gata2, Fli1 triad module comprises of multiple positive feedback loops. Each member of the triad positively regulates the transcription of the other two by acting at the respective enhancer sites. In addition Gata2 and Fli1 positively regulate their own transcription. External signals are encoded into transcription factors Notch and Bmp4 act on the promoters of Gata2 and Gata2, Fli1 respectively. We use an ODE model to describe the dynamics of this module. In our model the likelihood of gene transcription is determined by the occupation state of the enhancer as well as the presence of external activating signals at the gene promoter. The probability of the enhancer being occupied is determined by the free energy of DNA binding of different regulatory proteins. Parameter estimation is done using the available experimental results for different combinations of enhancer elements.

III. Results

The estimation of free energies of regulator-DNA binding shows that the action of triad components at the enhancers is highly cooperative and explains the loss of enhancer function upon rearrangement of enhancer elements in the Scl enhancer [4]. The model shows that the module exhibits bistable behavior that is robust to variations in parameter values. The triad can be turned on to high state by transient signals such as Notch and Bmp4 as seen experimentally. The irreversible nature of the bistability reflects the commitment of cell fate that is characteristic of gene expression programs in lineage selection. The range of bistability for the module can be tuned within the cell by a putative activator of Scl transcription. No such tunable bistable behavior was observed with reduced modules.

IV. Conclusion

The mathematical model of the triad module offers significant insight into the function and design of this genetic circuit.

References

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