Novel positive feedback loop sets antigen dose-dependent threshold for T cell differentiation

Robert P. Sheehan[1], William F. Hawse[2], Robin E. C. Lee,[1] Penelope A. Morel[2], and James R. Faeder[1]

Antigen stimulation of the T cell receptor (TCR) in a naïve T cell triggers a complex network of signaling pathways that determine whether the cell becomes a tolerogenic T regulatory (Treg) or immunogenic T helper (T_H) cell. We have recently discovered a potential positive feedback loop involving Akt-mediated transcriptional downregulation of PTEN, a lipid phosphatase that opposes activation of Akt. To explore the effects of this feedback we developed a model of signaling downstream of the TCR, with a focus on the regulation of PTEN and Akt. This model recapitulates dose-dependent dynamics of PTEN and Akt activity and predicts a dose- and time-dependent threshold for TCR stimulation to drive the sustained Akt activity required for the differentiation and proliferation of T_H cells. The model also shows that sub-threshold signals lead to transient Akt activation, potentially leading to a Treg phenotype.

***Keywords* — T cell differentiation, rule-based modeling, bistability, parameter estimation, PTEN**

I. Background

THE proper differentiation of naïve CD4+ T cells into Treg and T_H populations is critical to immune function. Maintenance of T_H populations is needed to fight infection, while Treg populations are necessary to prevent autoimmune disorders. It has been shown that Treg induction can prevent the onset of type 1 diabetes in mice [1].

TCR signaling is an important regulator of differentiation outcome. Akt activation downstream of the TCR has been shown to correlate with T_H development [2,3]. One key regulator of Akt is the phosphatase PTEN, which inhibits Akt activity through upstream dephosphorylation of PIP3 [4], a phospholipid that recruits numerous signaling proteins to the plasma membrane. Regulation of PTEN involves both post-translational modifications [5] and a recently-identified transcriptional control circuit involving the transcription factor Foxo1, which is inactivated through phosphorylation by Akt, forming a positive feedback loop for Akt activation [6]. Mathematical modeling allows us to predict TCR-dependent regulation of PTEN activity and its effects on CD4+ T cell differentiation.

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[1]Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, PA, 15260. E-mail: rps32@pitt.edu, robinlee@pitt.edu, faeder@pitt.edu

[2]Department of Immunology, University of Pittsburgh, Pittsburgh, PA, 15260. E-mail: whawse@pitt.edu, morel@pitt.edu

II. Results

A. A detailed model of Akt activation dynamics recapitulates experiments results and reveals bistability

We have developed a rule-based model of Akt activation downstream of the TCR and calibrated it using Bayesian parameter estimation [7] augmented by parallel tempering [8]. The resulting parameterization reveals bistability in the system, with high-dose antigen stimulation leading to a sustained drop in PTEN levels, and a corresponding increase in Akt activity, which lead to T_H cell differentiation. We predict a bistable switch in the system, resulting in two stable states with high and low levels of PTEN respectively. The threshold of the switch is controlled by the strength and duration of TCR activation.

B. A second signal activating PI3K is necessary for full commitment and sustained PTEN suppression

Activation of PI3K through CD28 is required for commitment to the T_H phenotype following antigen removal. Commitment requires maintenance of high levels of Akt activity and suppression of PTEN. Varying levels of CD28 can change the level of antigen stimulation required to cross the threshold for T_H differentiation.

III. Conclusion

Using a combination of mathematical modeling and experiments in primary cells, we have identified PTEN opposition of Akt as a critical circuit in the differentiation of naïve CD4+ T Cells. TCR stimulation-dependent regulation of PTEN leads to a bistable switch influencing the differentiation commitment of these cells. We have also made predictions on the duration of antigen stimulation needed to induce commitment to an Akt-high state, which we are currently in the process of testing experimentally.

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