Logical Modeling of Peripheral T Cell Differentiation

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Abstract

Peripheral naïve T-cells can differentiate into several effector phenotypes, the relative proportions of which are critical for immune-related pathologies.

We present here a logical model of T-cell differentiation that dictates selection of the regulatory cell fate (Treg) versus the helper cell fate (Th).

Model simulation accurately recapitulates existing experimental results and suggests directions for new experiments.

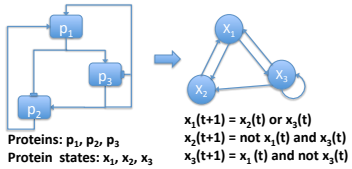
Motivation

Mechanisms involved in dendritic cell-mediated expansion of Treg cells relative to Th are not well understood. Recent results suggest that antigen dose is the primary determinant and that the Akt/mTor pathway plays a critical role [1-3]. Treg expansion is seen under conditions of low antigen dose [1], transient antigen dose [2] and inhibition of the Akt/mTor pathway [2,3].

Logical modeling enabled formal representation of current information in the literature about relationships between components of the TCR, PI3K and IL2R signal pathways. Simulations were done with asynchronous updating using BooleanNet [4].

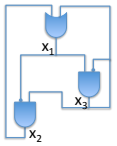
Logical Modeling & Simulation

Each biochemical component is modeled as a variable taking values 0 and 1, representing ON/OFF or HIGH/LOW. A logical rule indicates what the value of one component should be in the next time step depending on its relationship with other components.



Proteins: p_1, p_2, p_3
Protein states: x_1, x_2, x_3

$x_1(t+1) = x_2(t)$ or $x_3(t)$
$x_2(t+1) =$ not $x_1(t)$ and $x_3(t)$
$x_3(t+1) = x_1(t)$ and not $x_3(t)$



Models exhibit dynamic properties such as steady states and state cycles. Randomized rule updating causes probabilistic and not deterministic end points, i.e. multiple steady states from the same starting values.

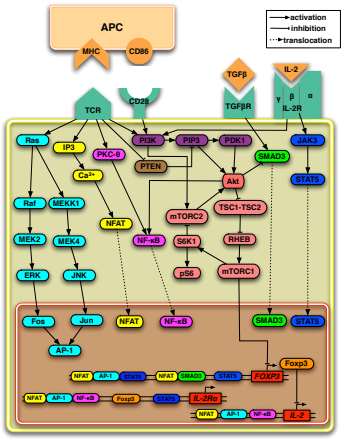
Model

Presentation of antigen by dendritic cells (APC) initiates signaling pathways through TCR and CD28 resulting in the activation of transcription factors AP-1, NFAT and NFκB.

Growth factor signaling from TGFβR and IL-2R results in activation of transcription factors SMAD3 and STAT5 respectively.

The transcription factors converge on the genes for Foxp3, IL-2 and IL-2Rα and initiate protein expression

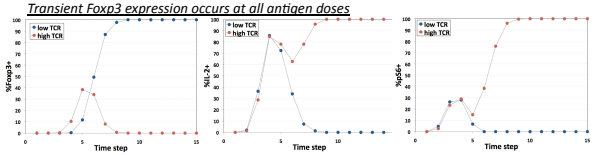
PI3K signaling via TCR and CD28 results in activation of mTORC1 via the Akt pathway which is antagonized by PTEN. mTORC1 inhibits Foxp3 expression.



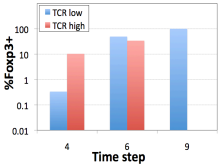
Results

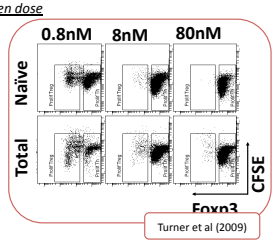
Antigen Dose Dependence: TCR High vs. TCR Low

Transient Foxp3 expression occurs at all antigen doses



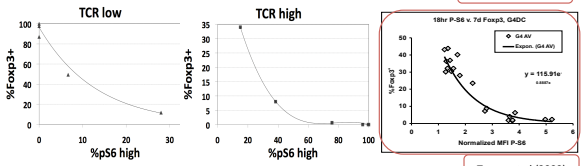
Treg expansion occurs at prolonged low antigen dose





Turner et al (2009)

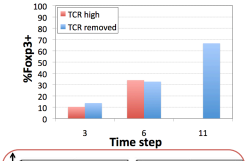
18 hour Akt expression correlates negatively with 7 day Foxp3 level

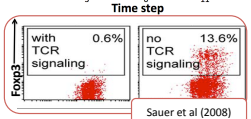


Turner et al (2009)

Transient TCR Signal

Treg expansion occurs when high antigen dose is removed after 18 hours

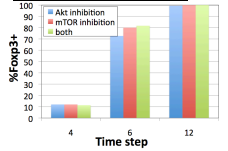


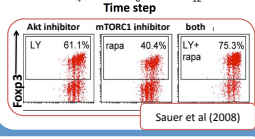


Sauer et al (2008)

Akt/mTor Inhibition

Treg expansion occurs when Akt and/or mTORC1 are inhibited





Sauer et al (2008)

Discussion

Methods
- Model is probabilistic and not deterministic.
- Dynamic behavior recovered.
- Logical models easily constructed, simulated and refined.
- Model behavior sensitive to composition of rules.
- Decisions for rule composition highlighted need for future experiments.

Results
- Important experimental results reproduced.
  - Transient Foxp3 expression at all antigen doses.
  - Treg expansion under
    - prolonged low antigen dose
    - transient high antigen dose
    - Akt/mTORC pathway inhibition
  - Akt expression negatively correlates with Treg cell fate.
- Race between Foxp3 induction by STAT5 and inhibition by mTORC1 activation controls final expression levels.
- Analysis identifies PTEN, STAT5 and events upstream of mTORC2 as critical nodes requiring further experimental evidence.

Future Directions

Experiments
- Differential PTEN and STAT5 expression in Treg and Th cells.
- Relationships between IL-2, TGFβ and PI3K pathways with regards to Foxp3 expression.

Modeling
- Model links upstream on mTORC2.
- Interactions of multiple cell types.
- Knock-outs, knock-ins and inhibitors.
- Updating biochemically fast and slow events differently.

References

1 Turner *et al. J Immunol (2009) vol. 183 (8) pp. 4895-903*
2 Sauer *et al. PNAS (2008) vol. 105 (22) pp. 7797*
3 Delgoffe *et al. Immunity (2009) vol. 30 (6) pp. 832-44*
4 Albert *et al. (2008) Source Code for Biology & Medicine*