Stochasticity and Bistability in TCR Signaling

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Short abstract **— The stochastic dynamics of T cell receptor (TCR) signaling are studied using a mathematical model intended to capture kinetic proofreading (sensitivity to ligand-receptor binding kinetics) and negative and positive feedback regulation. The model reproduces two key experimental observations: 1) robust responses to as few as a handful of ligands and 2) distinct responses to ligands that bind TCR with different lifetimes, and antagonism. Analysis of the model indicates that TCR signaling dynamics are marked by large stochastic fluctuations and bistability. Switch-like responses to signals enabled by bistability may aid T cells in making committed cell-fate decisions.**

Keywords **— TCR signaling, stochasticity, bistability.**

Activation of T cells is not only sensitive to minute amounts of peptide antigen but also selective, discriminating between foreign peptides, which must be recognized for immune defense, and self-peptides, which must be ignored to avoid autoimmunity. In proposed model of TCR signaling, discrimination between endogenous, antagonist and agonist peptides results from kinetic proofreading and negative and positive feedbacks [1-2]. Kinetic proofreading follows from the ordered sequence of reactions that occur at the TCR to induce T cell activation. TCR signaling is initiated by binding of peptide-MHC (pMHC) to TCR. Next Lck, a protein tyrosine kinase, binds to the cytoplasmic side of TCR and autophosphorylates at Y394 (Lck-Y). At this point a negative feedback is initiated: Lck-Y activates its own inhibitor, the protein tyrosine phosphatase SHP-1, phosphorylating it at Y564. Activated SHP-1 binds to TCR, dephosphorylates Lck-Y, and prevents its phosphorylation. If Lck-Y escapes dephosphorylation it sequentially phosphorylates two sites of the TCR to generate ppTCR, which initializes activation of a MAPK cascade, resulting in signal amplification and massive ERK activation. Activated ERK mediates a positive feedback, phosphorylating Lck at S59, which blocks its interaction with SHP-1 and thus inhibits the negative feedback loop.

A model encompassing the molecules and events just described contains 37 chemical species and 97 reactions, as summarized in **Fig. 1**. Two kinds of numerical simulations were performed: deterministic simulations using ordinary differential equations and stochastic simulations using the Gillespie algorithm [3].

The model exhibits three important features of T cell activation: high sensitivity, ability to discriminate between agonist and self peptides, and antagonism, inhibition of cell activity in the presence of antagonist peptides.

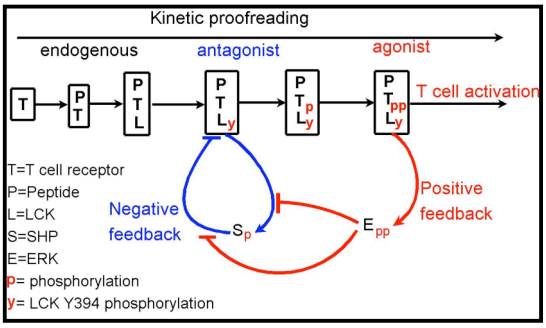

Fig. 1. Simplified diagram of the model

The interplay between negative and positive feedbacks also causes bistability. For an intermediate number of activating peptides, the system has two stable steady states, one with a low and the other with a high level of active ERK. The second state may be interpreted as a cytotoxic state that allows killer T cells to initiate death of an antigen-presenting cell. Because killer T cells decide the fate of scanned cells, bistability in their activation provides a way to minimize cell-fate ambiguity. As shown in **Fig. 2**, bistability also leads to marked differences between deterministic and stochastic trajectories. The latter may be more relevant for physiological conditions, under which T cell responses are usually elicited by a small number of foreign peptides.

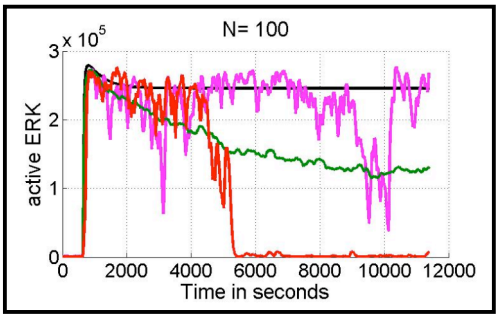

Fig. 2. Active ERK calculated in deterministic (black line) and stochastic (red and pink lines) simulations. The green line is the average over 100 stochastic trajectories. The deterministic trajectory tends to the steady state characterized by high level of active ERK, while the stochastic trajectories may jump between the two steady states.

References

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[3] Executable versions are available in Matlab and BioNetGen Language (see http://bionetgen.org) formats.

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