A Model for Early Events in T-cell Receptor Signaling

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***Short Abstract* — During T lymphocyte activation, many proteins are phosphorylated and dephosphorylated on tyrosine residues. Through these modifications, proteins gain or lose the ability to bind other proteins containing SH2 domains or gain or lose the ability to catalyze reactions. To better understand the dynamics of tyrosine phosphorylation, we have developed a rule-based model of early events in T-cell receptor signaling in Jurkat T cells. Proteins and protein interactions were included in the model based on published literature and temporal phosphoproteomic data. Our model accounts for 20 proteins and 22 tyrosine phosphorylation sites. Time courses of tyrosine phosphorylation predicted by the model are consistent with measured time courses. This model represents an effort to link quantitative proteomics data to detailed computational modeling. The model constitutes a detailed hypothesis about the mechanism of T-cell activation triggered by cross-linking of TCR/CD3 and CD28.**

***Keywords* — T cell activation, TCR, CD28, phosphorylation, proteomics, pathway simulation**

I. Purpose

THE T-cell activation process has been studied intensively by experimental immunologists. Their studies revealed that tyrosine phosphorylation plays important roles in the process [1]. Tyrosine phosphorylation allows proteins to bind SH2 domains [2] and regulates enzyme activities [3]. Through a complex network of protein interactions and enzyme activities, signals from the T cell receptor (TCR) and its co-receptor (CD28) are transduced to the inside of a cell. Despite the tremendous knowledge collected by experimental biologists, how the initial signaling orchestrates in T-cell activation is still not completely characterized.

To gain a better understanding of the initial events in T-cell activation, we developed a detailed computational model. This model is detailed in that: (1) Each tyrosine residue and its position in a protein is tracked in the model; (2) Interactions among the proteins in the model are based on an extensive literature review; (3) All the interactions are defined using rule-based modeling [4].

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II. The Model

The model specification is written in the BioNetGen language [5]. About 20 protein species with 22 tyrosine phosphorylation sites and more than 100 reaction rules are included in the model. Reaction rules in the model include receptor activation reactions, enzyme substrate reactions, and scaffold protein bindings. The model is simulated using the network-free simulation algorithm implemented in the RuleMonkey program [6].

III. Conclusion

Simulation results from our model are compared to quantitative site-specific proteomics data generated from our collaborators. The current model can reproduce the phosphorylation time courses from the receptor to ZAP-70. This model represents an effort to link quantitative proteomics data to detailed computational modeling.

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