Modeling phosphorylation dynamics of the T-cell receptor signaling network

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***Short Abstract* — Recognition of peptide antigens by the T-cell receptor (TCR) initiates intracellular signaling events that can culminate in T-cell activation, an essential component of the adaptive immune response. Early events following TCR stimulation are relayed in large part through phosphorylation of tyrosine residues in signaling proteins. These site-specific phosphorylation events have been identified and monitored quantitatively using time-resolved mass spectrometric techniques. The resulting phosphoproteomic data reflect the kinetics of molecular interactions in this signaling system. Thus, modeling of chemical kinetics can be a means of data analysis. To this end, we have developed a computational model of early events in TCR signaling that encompasses twenty proteins and aims to reproduce time courses of phosphorylation measured experimentally. To enable development and simulation of this large-scale model, we have applied rule-based representations of molecular interactions and algorithms for agent-based simulation consistent with physicochemical principles. The model can be used to provide a mechanistic interpretation of temporal phosphoproteomic data, to predict consequences of perturbations on the system, and to visualize and annotate available knowledge about TCR signaling.**

***Keywords* — rule-based modeling, cell signaling, proteomics, mass spectrometry, T-cell receptor, CD28, immunoreceptors**

I. Background

Receptors and co-receptors on the surface of a T-cell can interact with ligands and initiate intracellular signaling. Signals are transmitted through phosphorylation and dephosphorylation of tyrosine residues, thereby regulating protein-protein interactions and catalytic activities. Aspects of these signaling processes have been studied extensively, and a complex picture of molecular interactions has emerged. To synthesize available knowledge and develop a mechanistic understanding of how the constituent parts of a signaling system work together, there is a need for quantitative characterization of signaling events through integrated experimental and computational approaches.

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II. Results

A. Phosphoproteomics

Mass spectrometry enables the simultaneous, unbiased detection of phosphorylation at a large number of specific amino acid residues [1]. In a time-resolved phosphoproteomic study of T cells during the first minute following receptor cross-linking, regulated phosphorylation of 280 sites in more than 70 proteins was detected. Of these sites, a subset was selected to guide construction of a mechanistic model. Our goal in modeling is to capture the interactions needed to reproduce these time courses.

B. Model development

The model has been developed using a rule-based approach [2], which enables specification and simulation of models that imply large reaction networks. This approach is well-suited to modeling of cell signaling systems. In short, proteins are represented as structured objects that contain components (e.g., domains), and rules specify the necessary and sufficient conditions required of components for an interaction to occur. Rules were formulated based on an extensive data-guided literature search.

C. Model simulation, visualization, and annotation

The model is simulated using network-free methods, which are algorithms for agent-based simulation consistent with the law of mass action [3]. Simulation results show agreement with the experimental data that guided model construction. The model is annotated and visualized using recently proposed conventions [4] to facilitate model exchange.

III. Conclusions

Temporal phosphoproteomic data guided development of a rule-based model of early events in T-cell receptor signaling; the model can in turn reproduce experimental observations. This work links quantitative experimentation to detailed computational modeling, and represents an approach that can be used to elucidate design principles of cell signaling systems.

References

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