Modeling the FcεRI signaling cascade: from receptor aggregation to the oligomerization of the scaffolding protein LAT

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***Short Abstract* — The aggregation of the high affinity receptor, FcεRI, on mast cells and basophils initiates a cell signaling cascade that often results in the release of histamine containing granules and the production of other mediators of anaphlaxis. We extend the model of Faeder et al. [1], which describes the early signaling events mediated by FcεRI, to encompass the kinetics of phosphorylation and aggregation of the scaffolding protein LAT (Linker for the Activation of T cells). Upon phosphorylation LAT becomes a major hub in the FcεRI signaling network. The model allows us to study the poorly understood mechanism by which receptor aggregation leads to LAT phosphoyrlation and serves as a platform for including additional elements of the signaling cascade.**

I. Motivation

SIGNALING through the high affinity receptor for IgE, FcεRI, is responsible for many of the symptoms of allergy and allergic asthma. FcεRI is expressed on mast cells and basophils. Signaling by these receptors is triggered by ligand-induced receptor aggregation. The role of receptor aggregation in cell signaling is to cause the cytoplasmic domains of aggregated receptors to remain in proximity for times much longer than random motions of diffusing receptors permit and, thus, to promote cell-signaling cascades. Aggregation of nonreceptor molecules, such as the linker for the activation of T cells, also plays a role in propagating signaling reactions [2]. LAT is a major signaling hub in reaction networks initiated by the activation of FcεRI on mast cells and T cell receptors on T cells. Aggregation of LAT is mediated by the formation of a 2:1 complex between the adaptor protein Grb2 and the nucleotide exchange fa[1]ctor SOS1. LAT has a variable valence depending on the number of tyrosines that are phosphorylated. The phosphorylation of LAT tyrosines is catalyzed by the activated forms of the cytosolic protein tyrosine kinase Syk, which is complexed with FcεRI.

II. Purpose

We propose a kinetic model of FcεRI-mediated signaling, beginning with the antigen-induced crosslinking of FcεRI, followed by activation of Syk, phosphorylation of LAT tyrosines by activated forms of Syk, and culminating with the aggregation of LAT by Grb2-SOS1-Grb2 complexes. We aim to predict the effect of dynamical variation of the LAT valence on the overall kinetics of LAT aggregation and investigate the mechanism of LAT phosphorylation by Syk.

Acknowledgements: This work was funded by NIH grant R37 GM35556-25.

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III. Hybrid model

Modeling of signal-transduction systems is challenging, in part because the molecular interactions occurring in these systems have the potential to generate large numbers of molecular complexes. Developing the model for FcεRI and LAT-mediated signaling, we use a hybrid approach, which allows us to overcome the challenge of reaction network generation and to reduce the overall computational cost. We assume homogeneity of a membrane compartment; diffusion effects associated with two-dimensional binding and dissociation reactions are taken into account as corrections to the rate constants [3]. Our approach combines a system of ODEs for predicting the dynamics of activated FcεRI-Syk complexes [1] with an agent-based stochastic algorithm for modeling aggregation of LAT. The stochastic part of the model is based upon our recently developed rule-based kinetic Monte Carlo (KMC) method that allows one to fully account for all of the molecular complexes arising from multivalent interactions [4]. We have recently applied this method to simulate FcεRI aggregation by a trivalent ligand [5] and LAT oligomerization by a Grb2-SOS1-Grb2 complex [6]. The preliminary model of LAT-Grb2-SOS1 interactions, however, assumed a fixed valence of LAT.

IV. Preliminary conclusions

The valence of LAT, which ranges from zero to three, is critical in determining the nature of aggregation. A gel-like phase can only be observed for valence three. The realistic model developed here sheds the light on how the antigen-induced receptor crosslinking initiates the time-dependent aggregation of LAT, which is responsible for sustaining and amplifying downstream signaling. We compare our simulation results with recent experimental data for the rates of protein dephosphorylation [7] and LAT clustering [8].

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