# How does a mast cell distinguish between two different extracellular stimuli that cause the same extent of receptor cross-linking?

Ambarish Nag[1], James R. Faeder[2], and Byron Goldstein[1]

***Short Abstract* — We explain using a previously-unknown mechanism how mast cells and basophils stimulated through the FcεRI-mediated signaling cascade may respond differentially to two different allergen concentrations that produce the same levels of receptor cross-linking.**

***Keywords*—mast cells, basophils, allergic response, allergens, Syk activation, kinetic effects**

MAST cells and basophils play an essential role in producing allergic responses [1]. Allergic individuals produce IgE that is specific for the multivalent foreign allergens that trigger their allergic responses. IgE binds with high affinity to a monovalent receptor, FcεRI, expressed on basophil and mast cell surfaces. The exposure to the allergen induces IgE to aggregate on the surfaces of these cells, and this cross-linking of FcεRI-bound IgEs by the allergen excites a signaling network that results in the release of preformed granules and newly synthesized mediators of anaphylaxis [2].

Faeder et al. have developed a detailed mathematical model [3] of the FcεRI-mediated signaling cascade up to the activation of a tyrosine kinase called Syk [3]. Syk is responsible for phosphorylating key tyrosine residues on an adaptor molecule called LAT (Linker for Activation of T cells), which is essential to mast cell function. Tyrosine-phosphorylated LAT acts as a scaffold for other signaling molecules that are responsible for $Ca^{2+}$ influx that results in cellular degranulation. Thus, it is a reasonable first approximation to use Syk activation as a metric for the extent of FcεRI-mediated signaling.

Intuitively, the variation of Syk activation with equilibrium extracellular allergen concentration should be qualitatively similar to the variation in the number of cross-linked receptors. For bivalent allergens interacting with IgE, the receptor cross-linking curve is bell-shaped and symmetric with respect to the free equilibrium allergen concentration. For many different physiological Syk expression levels, the Syk activation curve is also bell shaped, as expected, but the model predicts that for some Syk expression levels, the Syk activation curve can have two or even three peaks depending on the Syk expression level. To fully activate a Syk molecule requires it to be transphosphorylation by a second Syk molecule when each are bound to a receptor in a dimer cross-linked by a bivalent allergen. Hence, for limiting Syk concentration, an excess of receptor cross-links over Syk molecules at some free equilibrium allergen concentrations can lead to high-dose inhibition of Syk activation [4]. At other allergen concentrations, the extent of cross-linking is lower so that there is enough Syk to bind to all the cross-linked receptors. This differential behavior at different allergen concentrations gives rise to the bimodal/multimodal behavior of the Syk activation curve. We noticed that the Syk activation curves in Ref. [4] are slightly asymmetric, and subsequently found conditions that exhibit significant variations in Syk activation levels at different doses of allergen that give the same level of receptor cross-linking. This behavior is observed in both transient and steady state responses. In functional terms, this means that the cell could distinguish between two different concentrations of allergens that produce identical distributions of receptor aggregates. This effect is not due to a form of kinetic proofreading, because aggregate lifetimes are identical under both conditions. Rather, the high and low ligand doses differentially activate distinct paths leading to Syk activation by trans-autophosphorylation. The reaction path leading to greater Syk activation is consistent with the analysis in Ref. [5] of the relative importance of the different reaction paths from unphosphorylated cytosolic Syk to fully activated Syk. We will provide a detailed explanation of this mechanism in our presentation.

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[1]Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM . E-mail: ambarish@lanl.gov, bxg@lanl.gov

[2]Department of Computational Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA. E-mail: faeder@pitt.edu

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