A theoretical analysis of the potential influence of ITAM pairs on Syk recruitment dynamics

Ryan Suderman¹², Samantha L. Schwartz³⁴, Diane S. Lidke³⁴ and William S. Hlavacek¹²⁴

Short Abstract — Syk is recruited to FcεRI aggregates during antigen stimulation of mast cells. It is not known how the dynamics of recruitment influence the regulation of the immune response. Recent experimental data shows that a mutant form Syk has distinct ITAM interaction kinetics from wild-type Syk, though the measurements differ significantly. We developed a series of mathematical models to explore this behavior, and found that the simplest model consistent with experimental observations explicitly considers pairs of ITAMs where Syk’s tandem SH2 domains can bridge the ITAMs.

Keywords— mast cell signaling, kinetic proofreading, dynamical systems biology, rule-based modeling, ITAM pairs

I. BACKGROUND

The immune response in mast cells relies on antigen-stimulated aggregation of the FcεRI receptor and recruitment of spleen tyrosine kinase (Syk) to the receptors’ immunoreceptor tyrosine-based activation motifs (ITAM). Syk is responsible for propagating downstream signaling, resulting in the release of histamine into the local environment, an event called degranulation [1].

Recently, Feng & Post showed that in vitro interaction lifetimes between individual ITAM peptides and a mutant form of Syk (Y130E) is an order of magnitude smaller than that for wild-type (WT) Syk [2]. Schwartz et al. found that membrane-localization lifetimes of wild-type (WT) and Y130E Syk in sensitized mast cells exposed to DNP-BSA show a similar trend, but with longer lifetimes and only a 30% decrease in Y130E Syk lifetime compared to WT Syk [3]. However, this relatively small change in lifetime completely eliminates mast cell degranulation and results in a variable reduction of Syk autophosphorylation at certain tyrosine residues (Y317, Y342, Y525/6) [3].

II. RESULTS

We first built a simple kinetic proofreading model using the in vivo lifetime parameters. However, the ratio of Y130E to WT Syk ITAM-binding lifetimes is sufficiently small that the model cannot reasonably capture the fold-change in Syk autophosphorylation observed in the mast cell system. Mechanistic models considering Syk recruitment to individual ITAMs also cannot reproduce the in vivo observations.

A. ITAM bridging

We therefore examined an alternative hypothesis using a series of rule-based models. One feature of immunoreceptors (e.g. Fc receptors, TCR, BCR) is the presence of paired ITAMs [4]. We posited that in vivo ITAM-binding lifetimes could be longer than those observed in vitro if Syk’s tandem SH2 domains could bridge the paired ITAMs. With a model using the in vitro kinetic parameters characterized by Feng & Post for interactions between individual ITAMs and Syk, we fit the parameters governing the proposed bridging interactions and found an ensemble of parameters consistent with both the in vivo and in vitro kinetic observations.

B. Differential tyrosine phosphorylation

To capture the observed fold change in phosphorylation, we further developed our model to include Syk auto-phosphorylation at residues Y317, Y342 and Y525/6. These sites also exhibit differential phosphorylation upon exposure to kinase inhibition [5], suggesting that they have distinct relative rates of phosphorylation. Assuming that phosphorylation of bridged Syk is distinct from single ITAM-bound Syk, our model captures the observed reduction in phosphorylation given Y130E Syk ITAM-binding lifetimes that are consistent with experiment.

III. CONCLUSION

Mathematical modeling shows that the classical picture of Syk binding a single ITAM, together with intra-aggregate trans autophosphorylation cannot capture observed lifetime and phosphorylation data in [3,5]. Our analysis reveals that ITAM pairing in immunoreceptors may be critical in understanding the membrane-proximal dynamics of the immune response.

REFERENCES