Mono and Multivalent Ligation of BCR Exhibit Differential Dependence on Syk and Src kinases

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***Short Abstract* — The Src and the Syk family kinases have overlapping role in B cell signaling. Syk can phosphorylate the BCR ITAMs, which are the primary substrate of Src kinases. With the aid of computation modeling and experiments we addressed the role of Syk in BCR signaling. Our results indicate that a positive feedback mechanism enables Syk to substantially compensate for Src in the presence of spatial clustering of BCRs induced by multimeric ligands. In the absence of BCR clustering both Syk and Src are required for B cell activation.**

***Keywords* — B cell signaling, BCR clustering, Syk and Src kinases in B cell, Computational modeling, Systems Biology.**

I. Overlapping Roles of Syk & Src Kinases In B cells.

Activation and signal transduction in lymphocytes such as B and T cells require the action of both Src and Syk kinases. Upon antigen ligation of B cell receptors (BCRs), Src family kinases phosphorylate BCR associated ITAMs. Phosphorylation of the ITAMs leads to the recruitment of Syk via its tandem SH2 domain, relieving it of auto inhibition and consequently enabling Syk to phosphorylate BCR associated ITAMs and initiate BCR signaling. B cells, unlike T cells, can function independently of Src kinases but have an absolute requirement for Syk kinases [1]. It has been shown that Syk can directly phosphorylate ITAMs in the absence of Src kinases and its function is regulated by a positive feedback [2, 3]. These observations beget two important questions: i) How does BCR signaling remain largely intact in the absence of Src family kinases? ii) Why B cells contain Src kinases when Syk can also activate ITAMs?

II. Computational Model and Prediction

We specifically modeled the interaction of soluble dimeric and monomeric HEL antigens with the BCRs using a space resolved continuous time Monte Carlo simulation. We have assumed that the BCR-dimeric HEL interaction induce BCRs to cluster, whereas the BCR-monomeric HEL interaction do not lead to substantial BCR clustering. Our simulations predict that in the presence of BCR microclusters, the Syk positive feedback alone is fully capable of compensating for the lack of Src kinase and successfully trigger BCR signaling [4]. If however the BCRs fail to cluster, the Syk feedback is incapable of restoring BCR signaling in the absence of the Src kinase [4].

III. Experiments and Validation

Our experiments validate our assumptions and show that Syk can indeed restore ITAM phosphorylation in a SH2 domain dependent way in heterologous cells treated with Src inhibitor. Moreover we show that MD4 BCR transgenic system expressing monoclonal BCRs when treated with dimeric sHEL mobilizes Ca^{++} even in the presence of Src inhibitor PP2, albeit for a time delay [4]. Monomeric HEL however, fails to mobilize Ca^{++} in MD4 cells substantiating our claim that only in the presence of dimeric sHEL induced BCR clustering can the Syk feedback effectively compensate for Src kinase [4].

IV. Conclusion

Our results indicate that both the BCR clustering and the Syk positive feedback work in tandem to recuperate for the loss of Src kinase. Src kinase in turn ensures a rapid and sensitive response to weak ligands where Syk positive feedback alone proves to be ineffective.

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