

Investigation of the roles of Src family tyrosine kinases in immune response signaling and their redundancy: focus on B cell antigen receptor signaling

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Abstract

Mammalian immune system combats foreign antigens by triggering complex signaling responses in immune cells. Early signaling responses in immune cells are governed by Src family protein tyrosine kinases (SFKs) following aggregation of cell-surface receptors by antigens. Because of their homologous structures and similar interactions, functional roles of the SFKs are thought to be redundant. In this talk, I will discuss our recent work, where we have dissected the roles of two SFKs, Lyn and Fyn, which activate B cell receptor (BCR) signaling.

BCR signaling encompasses two feedback loops emanating from Lyn and Fyn. Positive feedback arises from SFK-mediated *trans* phosphorylation of BCR and receptor-bound Lyn and Fyn, which increases the kinase activities of Lyn and Fyn. Negative feedback arises from SFK-mediated *cis* phosphorylation of the transmembrane adapter protein PAG1, which recruits the cytosolic protein tyrosine kinase Csk to the plasma membrane, where it acts to decrease the kinase activities of Lyn and Fyn. To study the effects of the positive and negative feedback loops on the dynamical stability of BCR signaling and the relative contributions of Lyn and Fyn to BCR signaling, we developed a rule-based predictive model for early events in BCR signaling. The model encompasses membrane-proximal interactions of six proteins: BCR, Lyn, Fyn, Csk, PAG1, and Syk, a cytosolic protein tyrosine kinase that is activated as a result of SFK-mediated phosphorylation of BCR. The model is consistent with known effects of Lyn and Fyn deletions. We find that BCR signaling can generate a single pulse or oscillations of Syk activation depending on the strength of antigen signal and the relative levels of Lyn and Fyn. We also show that bistability can arise in Lyn- or Csk-deficient cells.

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