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A rule-based model for early events in B cell antigen receptor signaling

B cell antigen receptor (BCR) signaling regulates the activities and fates of B cells. Here, we present a rule-based model for early events in BCR signaling that encompasses membrane-proximal interactions of BCR, two membrane-tethered Src-family protein tyrosine kinases, Lyn and Fyn, the adaptor protein PAG, and two cytosolic protein tyrosine kinases, Csk and Syk. The signaling is triggered by aggregation of the BCR by foreign antigens, which increase the rate of BCR-Src kinases interactions. The interactions involve two feedback loops: a positive feedback loop acting on a short time scale and a negative feedback loop acting on a longer time scale. The positive feedback loop arises because of the way that the two Src-family kinases, Lyn and Fyn, interact with the two signaling chains of the BCR complex, Igα (CD79A) and Igβ (CD79B). Lyn and Fyn constitutively associate with BCR via low-affinity interactions and trans-phosphorylate tyrosine residues in the immunoreceptor tyrosine-based activation motifs (ITAMs) of Igα and Igβ in neighboring receptors within antigen-induced clusters of BCR. These sites of phosphorylation then serve as high-affinity docking sites for the SH2 domains in Lyn and Fyn, which recruit more Lyn and Fyn to BCR clusters. Lyn and Fyn also undergo autophosphorylation within antigen-induced clusters of BCR, which upregulates their kinase activities. The negative feedback loop is mediated by PAG, which associates with Lyn and Fyn in a phosphorylation-dependent manner. PAG serves as a docking site for Csk, which mediates the phosphorylation of a C-terminal regulatory tyrosine residue found in both Lyn and Fyn. Phosphorylation of this residue enables an intramolecular interaction that downregulates Lyn/Fyn kinase activity. The model makes the distinction between the two Src kinases, Lyn and Fyn. Whereas Lyn is allowed to phosphorylate PAG at all tyrosine residues, Fyn may not phosphorylate its own binding sites on PAG due to allosteric constraints. This distinguishes Lyn as the only Src kinase capable to induce the negative feedback in the system. A dynamical stability analysis of the model reveals that the BCR circuit can display two interesting behaviors. Bistability can be expected in PAG -/-, Csk -/-, and Lyn -/- cells, whereas oscillatory pulse-like responses to BCR clustering can be expected in cells with the negative feedback loop intact (wild-type cells and Fyn -/- cells) under some conditions. The qualitative behaviors predicted

by the model are consistent with the known behaviors of Lyn and Fyn deficient cells.

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