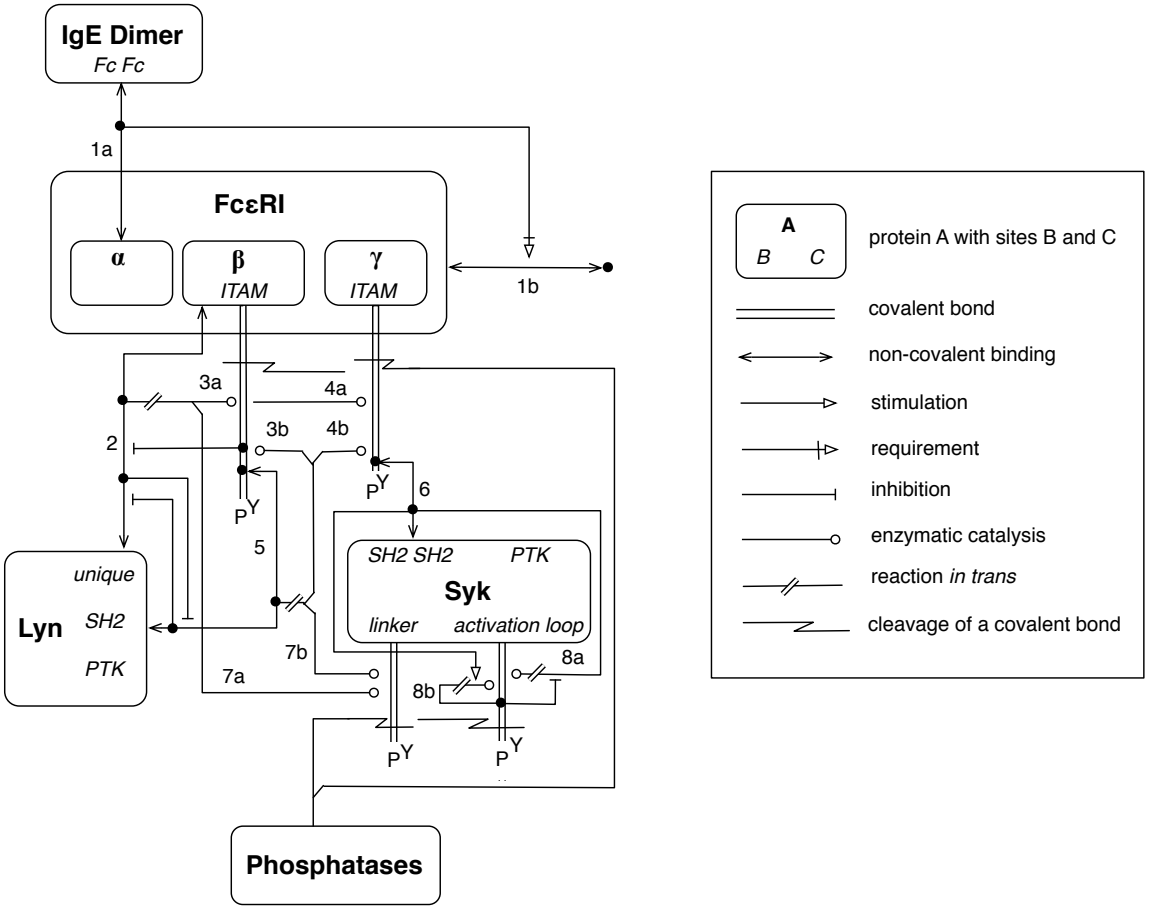
Appendix S2: MIM annotation



This MIM (Fig. 3 in the main text) is intended to be read using the 'combinatorial interpretation,' meaning that all possible interactions do occur unless otherwise specified. A legend is included here to explain the MIM notation.

General notes: The high-affinity IgE receptor (FcεRI) on rat basophilic leukemia (RBL) cells is tetrameric, being composed of polypeptide chains FcεRIα, FcεRIβ, and a homodimer of disulfide-linked γ chains. The receptor dimerizes upon interaction with a chemically crosslinked dimer of IgE antibodies. The β and γ chains are phosphorylated by Lyn. Lyn kinase activity is different depending on whether it is bound to the receptor via its unique domain or its SH2 domain. Syk can be phosphorylated in its linker region, which has no effect on its kinase activity. Syk can also be phosphorylated in its activation loop, which increases its kinase activity. The arrows labeled 1a, 1b, 2, etc. in the MIM (Fig. 3 in the main text) are annotated below. The annotation presented below is mainly intended to explain our use of MIM

notation. For additional details about the biological knowledge captured in this diagram, see Appendix S1 (ESI).

1a: Ligand binds the α chain of the receptor.

1b: Receptor dimerizes.

A receptor must be bound to a ligand for dimerization to occur so a requirement arrow points from the ligand-receptor binding arrow (Arrow 1a) to the receptor dimerization arrow (Arrow 1b).

2: The unique domain of Lyn binds the unphosphorylated β chain.

For this interaction to occur, the β chain must be unphosphorylated, so an inhibition arrow points from the β pY glyph to Arrow 2. Also, the SH2 domain of Lyn must be free, so another inhibition arrow points from Arrow 5 (Lyn binding via SH2 domain) to Arrow 2. The interactions represented by Arrows 2 and 5 are mutually exclusive.

3a: Lyn that is bound by its unique domain transphosphorylates β.

Lyn phosphorylates the β chain of an adjacent receptor in a receptor dimer, not the receptor to which Lyn is bound. To indicate that phosphorylation is *trans*, the *trans* symbol is used; this symbol appears in the MIM as two parallel diagonal line segments. For the interaction represented by Arrow 3a to occur, Lyn must be bound via its unique domain, so the catalysis arrow originates from Arrow 2.

4a: Lyn that is bound by its unique domain transphosphorylates γ.

The use of MIM notation for this interaction is the same as for the interaction represented by Arrow 3a.

5: The SH2 domain of Lyn binds phosphorylated β.

The β ITAM must be phosphorylated for this interaction to occur, so Arrow 5 points to the β pY glyph. Also, the unique domain of Lyn must be free, so an inhibition arrow points from Arrow 2 (Lyn binding via unique domain) to Arrow 5. The interactions represented by Arrows 5 and 2 are mutually exclusive.

3b: Lyn that is bound by its SH2 domain transphosphorylates β.

The *trans* symbol is used for the same reasons as for Arrow 3a. Lyn must be bound via its SH2 domain, so the catalysis arrow originates from Arrow 5. Lyn bound via its SH2 domain has higher activity than Lyn

bound via its unique domain.

4b: Lyn that is bound by its SH2 domains transphosphorylates γ.

The use of MIM notation for this interaction is the same as for the interaction represented by Arrow 3b.

6: The tandem SH2 domains of Syk bind phosphorylated γ.

These two domains are lumped together in the model, so only one binding arrow is shown in the MIM.

7a: Lyn that is bound by its unique domain transphosphorylates the linker region of Syk.

The unique domain of Lyn must be bound to β, so the catalysis arrow originates from Arrow 2.

7b: Lyn that is bound by its SH2 domain transphosphorylates the linker region of Syk.

The Lyn SH2 domain must be bound to β, so the catalysis arrow originates from Arrow 5.

8a: Syk transphosphorylates the activation loop in another molecule of Syk.

The enzyme in this interaction is a copy of Syk that is unphosphorylated in its activation loop. The *trans* symbol is used because Syk catalyzes phosphorylation of another molecule of Syk. Syk must be bound to γ, so Arrow 8a originates from Arrow 6. Phosphorylation of the activation loop inhibits the interaction represented by Arrow 8a because this interaction involves unphosphorylated Syk as the enzyme.

8b: Activated Syk transphosphorylates the activation loop in another molecule of Syk.

The enzyme in this interaction is Syk that has been phosphorylated in its activation loop (in other words, activated Syk). Thus, as indicated in the MIM, phosphorylation in the activation loop brings about *trans*-phosphorylation of another molecule of Syk. Both Syk molecules must be bound to γ, so an activation arrow points from Arrow 6 to Arrow 8b.

Dephosphorylation.

Jagged lines represent dephosphorylation reactions. All phosphotyrosines are dephosphorylated by unspecified phosphatases, which are assumed to be available in excess.