

Syk

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Overview

Syk (spleen tyrosine kinase) is a non-receptor protein tyrosine kinase that has, at the N-terminus, a tandem pair of Src homology 2 (SH2) domains separated by a long linker (linker B) from the C-terminal catalytic domain. Syk is one of two members of the Syk-family of kinases, the other being ZAP-70. An alternatively spliced variant of Syk, SykB, lacks a stretch of 23 amino acids from linker B. Syk prefers to phosphorylate substrates on tyrosines surrounded by acidic amino acids. Syk is expressed in most hematopoietic cells including B cells, thymocytes, erythrocytes, monocytes, macrophages, leukocytes, natural killer cells, eosinophils, mast cells and basophils, but is largely absent from mature T cells. It is also expressed in epithelial cells and in some neuron-like cells, hepatocytes, and endothelial cells. SykB is found most abundantly in bone marrow-derived B cells and epithelial cells.

In hematopoietic cells, Syk is required for transducing signals from a wide variety of cell surface receptors involved in the recognition of antigens or antigen-antibody complexes. In Syk-deficient mice, B cell development is blocked due to a lack of signaling from pre-B and B cell antigen receptors. Syk-deficient mast cells are unable to degranulate when triggered through the high-affinity IgE receptor, FcεRI. Phagocytosis through Fcγ receptors is blocked in Syk-deficient macrophages as is the FcγR-stimulated production of reactive oxygen species. FcR-dependent immune complex internalization is blocked in dendritic cells from Syk-deficient mice as is the activation and aggregation of platelets via the collagen receptor. Syk associates with the B cell and T cell antigen receptors, FcεRI, FcγRI, FcγRIIa, FcγRIIIa, NK cell activating receptors and collagen receptor through

the binding of its tandem SH2 domains to a conserved pair of tyrosines present within an immunoreceptor tyrosine-based activation motif (ITAM) found on the cytoplasmic tails of receptor components. ITAMs bear the consensus sequence E/DXXYXX(L/I)X₆₈YXX(L/I) and bind Syk when both tyrosines are phosphorylated, typically by a Src-family kinase in conjunction with Syk, itself. In addition, Syk associates with β-integrins and the receptors for IL-2, G-CSF, GM-CSF, IL-3, IL-5, IL-15, and tumor necrosis factor (TNF). In Syk-deficient mice, integrin-dependent signaling in monocytes and neutrophils is defective. Syk-deficient mice exhibit a perinatal lethality resulting from a failure of the circulatory and lymphatic systems to separate during development.

Syk is localized in resting cells in both the nucleus and cytoplasm and is recruited from both compartments to the site of the aggregated, ITAM-containing receptor. The binding of Syk to phosphorylated ITAMs on cross-linked receptors leads to its activation and its phosphorylation on multiple tyrosines. The phosphorylation of tyrosines in the activation loop of the catalytic domain are important for receptor-mediated signaling. The phosphorylation of linker B region tyrosines provides docking sites for downstream effectors that bear SH2 or related domains. The binding of c-Cbl, an E3 ubiquitin ligase, to phosphotyrosine-317 (mouse) inhibits Syk-dependent signaling. The C-terminal SH2 domain of the p85 subunit of phosphoinositide 3-kinase can also bind here. Tyrosines-342 and -346 constitute a multi-functional binding site that interacts with SH2 domains from the guanine nucleotide exchange factor, Vav1, phospholipase C-γ (PLCγ) and the Src-family kinase, c-Fgr. Vav1 can bind phosphotyrosine-342 alone while PLCγ binds only when

both tyrosines are phosphorylated. Syk also binds CrkL and Gab2.

Syk is expressed in normal breast epithelial cells and in relatively benign breast cancer cells, but is missing from highly metastatic cells due to gene methylation. Re-expression of Syk in malignant breast cancer cells reduces their tumorigenicity, decreases cell motility and enhances cell-cell adhesion. Syk functions, in part, through its ability to associate with and inhibit signaling from the EGF receptor.

Syk

FAMILY MEMBERS	Syk	ZAP-70
OTHER NAMES	Spleen tyrosine kinase	Syk-related protein kinase; SRK
MOLECULAR WEIGHT/STRUCTURAL DATA	72 kDa; 635 aa (human), 629 aa (mouse)	70 kDa; 619 aa
ISOFORMS	SyxA, SykB	Not known
SPECIES	Human, mouse, rat, pig	Human, mouse
DOMAIN ORGANIZATION	C-terminal SH2 domain, N-terminal SH2 domain, kinase domain	C-terminal SH2 domain, kinase domain, N-terminal SH2 domain
PHOSPHORYLATION SITES (MOUSE)	Tyr ¹³⁰ , Tyr ²⁹⁰ , Tyr ³¹⁷ , Tyr ³⁴² , Tyr ³⁴⁶ , Tyr ³⁵⁸ , Tyr ⁵¹⁹ , Tyr ⁵²⁰ , Tyr ⁶²³ , Tyr ⁶²⁴	Tyr ¹²⁶ , Tyr ²⁹² , Tyr ³¹⁵ , Tyr ³¹⁹ , Tyr ⁴⁹² , Tyr ⁴⁹³
TISSUE DISTRIBUTION	Spleen, thymus, peripheral blood cells, mammary gland, liver, lung	T cells, natural killer cells
SUBCELLULAR LOCALIZATION	Cytoplasmic membrane, cytoplasm, nucleus	Cytoplasmic membrane, cytoplasm
BINDING PARTERS/ ASSOCIATED PROTEINS	NFAM-1, Cbl, FcR γ , CD3 ζ , CD69a, CD69b, DAP-12, β -integrins, PLC γ , Vav, PI3K, c-Fgr	NFAM-1, CBL, SLA, CD3Z
UPSTREAM ACTIVATORS	TNF receptor, β -integrins, Lyn, Fc ϵ RI, Fc γ RI, Fc γ RIIa, Fc γ RIIIa, BCR, TCR, GM-CSF, G-CSF	TCR-Z, LCK
DOWNSTREAM ACTIVATION	PLC γ 2, Vav, PI3K, Btk	Not known
SUBSTRATES	Vav, Cbl, PLC γ , HS1, Band 3, α -tubulin, BLNK/SLP-65, LAT, 3BP2, Cortactin, SH3P7, B cell receptor, PKC β , PKC α , BCAP, Fc γ R γ -chain, Btk, CD19	Not known
ACTIVATORS	Not known	Not known
INHIBITORS	Piceatannol (P0453), ER-27319 (E0656), BAY 61-3606, Syk inhibitor 574711	Not known
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	B cell development and activation, FcR-mediated phagocytosis, platelet activation, eosinophil activation and survival, mast cell activation, neutrophil/ monocyte spreading and migration, epithelial cell adhesion and motility	T cell activation regulator
DISEASE RELEVANCE	Asthma, allergy, leukemia, breast cancer	Human immunodeficiency, selective T-type defect

FOOTNOTES

Syk

Abbreviations:

3BP2: SH3 binding protein 2

574711: 3-(1-Methyl-1H-indol-3-yl-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide

Band 3: Erythrocyte anion transport channel

BAY 61-3606: 2-[7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino]-nicotinamide dihydrochloride

BCAP: B cell adaptor protein

BCR: B cell antigen receptor

BLNK: B cell linker protein

Btk: Bruton's tyrosine kinase

Cbl: Casitas B-lineage lymphoma oncoprotein

c-Fgr: Cellular homolog of transforming protein of Gardner-Rasheed feline sarcoma virus

CrkL: v-Crk sarcoma virus CT10 oncogene homolog-like

EGF: Epidermal growth factor

ER-27319: 3,4-Dimethyl-10-(3-aminopropyl)-9-acridone oxalate

FcεRI: High affinity receptor for IgE

FcγR: Receptor for IgG

GAB2: Growth factor receptor binding protein-2 (Grb2)-associated binding protein-2

G-CSF: Granulocyte colony stimulating factor

GM-CSF: Granulocyte/macrophage colony stimulating factor

HS1: Hematopoietic specific protein-1

IL: Interleukin

ITAM: Immunoreceptor tyrosine-based activation motif

LAT: Linker of activated T cells

NFAM-1: NFAT activating molecule 1

NK: Natural killer

PI3K: Phosphoinositide 3-kinase

PKC: Protein kinase C

PLCγ: Phospholipase C-γ

SH2: Src homology 2

SH3P7: SH3 domain containing protein 7

SLP65: SH2 domain-containing leukocyte protein of 65 kDa

Syk: Spleen tyrosine kinase

TNF: Tumor necrosis factor

ZAP70: ζ chain associated protein of 70 kDa

FOOTNOTES