## Phylogeny

Spleen tyrosine kinase (SYK) belongs to the Tyrosine Kinase (TK) group, SYK/ZAP-70 family identified by kinome surveys (Patterson et al., 2015). Vertebrates encode a single paralog (ZAP-70) that shares tandem SH2-kinase architecture (Sada et al., 2001). Documented SYK/ZAP-70 orthologs occur in chicken, mouse, rat, frog, zebrafish, the cartilaginous fish Callorhinchus milii, and Drosophila melanogaster SHARK (Patterson et al., 2015). A lamprey sequence (Lj-Syk) containing both SH2 and kinase domains indicates that the family predates the jawed/jawless vertebrate split (Liu et al., 2015).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosyl-phosphate (Sada et al., 2001).

## Cofactor Requirements

Catalysis requires Mg²⁺, coordinated by Asp518 of the DFG motif in the active site (Atwell et al., 2004).

## Substrate Specificity

Peptide-array profiling shows a dominant −1 P-Y-x-R/K motif with Pro at −1 and basic residues at +2/+3 (Yaron-Barir et al., 2024). Acidic or bulky hydrophobic residues (Asp/Glu/Leu/Ile) are tolerated at −1; Glu is mildly preferred at +1, Pro at +3, while other positively charged residues are generally disfavoured (Hobbs et al., 2022). Recognition is further enhanced by “phospho-priming” when a phospho-Tyr/Thr is pre-existing at −1 or +2 (Yaron-Barir et al., 2024).

## Structure

The full-length protein is organised N-SH2 (~7-115) – inter-SH2 linker (A) – C-SH2 (~116-269) – interdomain B (~120 aa) – kinase domain (356-635) (Unknown Authors, 2009).  
• Tandem SH2 crystal structure (PDB 1A81) shows head-to-tail binding to a doubly phosphorylated ITAM peptide (Singh et al., 2012).  
• Kinase domain structures include apo (1XBA), imatinib-bound (1XBB) and staurosporine-bound (1XBC); despite being unphosphorylated, the kinase adopts an active DFG-in conformation with the activation loop partly disordered (Atwell et al., 2004).  
• A higher-resolution inhibitor complex (PDB 4PUZ) displays aligned hydrophobic spines and an ordered αC-helix (Singh et al., 2012).  
• Key catalytic residues: Lys402 (β3), Asp512 (HRD), Asp518 (DFG), and activation-loop Tyr525/Tyr526 (Atwell et al., 2004).  
• An EM model of the full-length protein reveals a closed “linker-kinase sandwich” that mediates autoinhibition; ITAM engagement or linker tyrosine phosphorylation opens the structure (Singh et al., 2012).  
• Imatinib binds in a unique cis orientation that exploits a collapsed ATP pocket, unlike its trans binding to ABL (Atwell et al., 2004).

## Regulation

Tyrosine phosphorylation  
– Src-family kinases (Lyn/Fyn/Src) phosphorylate receptor ITAMs, recruiting and activating SYK (Tohyama & Yamamura, 2009).  
– Autophosphorylation on Y131 reduces ITAM affinity (Unknown Authors, 2009).  
– Y317 creates a C-Cbl docking site, leading to ubiquitination (Mócsai et al., 2010; Rao et al., 2001).  
– Y342/Y346 recruit VAV1 and PI3K-p85 (Mócsai et al., 2010).  
– Y348/Y352 autophosphorylation stabilises the open state; PKCε limits their phosphorylation in human platelets (Buitrago et al., 2013).  
– Activation-loop Y525/Y526 autophosphorylation completes catalytic activation; SHP-1 (PTPN6) and TULA-2 remove these marks (Buitrago et al., 2013).  
– C-terminal Y624/Y625 fine-tune mast-cell signalling (de Castro et al., 2010).

Serine phosphorylation  
– PKC phosphorylates S297; PP2A reverses this modification. Sustained S297-P suppresses Y525/Y526 phosphorylation and activity (Makhoul et al., 2020).

Ubiquitination  
– Active SYK is poly-ubiquitinated by C-Cbl; specific lysine sites remain undetermined (Paolini et al., 2002; Buitrago et al., 2013).

Allosteric control  
– Activity can be triggered either by SH2-ITAM binding or by phosphorylation of linker tyrosines, providing “OR-gate” regulation between receptor engagement and intracellular priming (Mócsai et al., 2010).

## Function

SYK is highly expressed in B cells, early thymocytes, NK cells, mast cells, macrophages, neutrophils, dendritic cells, platelets and osteoclasts, with lower expression in some epithelial and fibroblast tissues (Mócsai et al., 2010; Singh et al., 2012).  
Upstream kinases: Lyn, Fyn, Src (ITAM phosphorylation); PKC and PP2A modulate serine phosphorylation (Tohyama & Yamamura, 2009; Makhoul et al., 2020).  
Major substrates/adaptors include BLNK, PLCγ2, LAT, VAV1, PI3K-p85, DEPTOR and LCP2 (Sada et al., 2001; Mócsai et al., 2010).  
Pathways: central effector in B-cell receptor (BCR), FcεRI/FcγR, platelet GPVI, C-type lectin and integrin outside-in signalling, controlling Ca²⁺ flux, degranulation, phagocytosis, platelet aggregation and cytokine production (Paolini et al., 2002; Tohyama & Yamamura, 2009; Antenucci et al., 2018).

## Inhibitors

– Imatinib: binds the active site in a unique cis orientation (Atwell et al., 2004).  
– Staurosporine: broad-spectrum ATP-competitive inhibitor (Atwell et al., 2004).  
– Fostamatinib (R788; active metabolite R406): low-nanomolar ATP-competitive inhibitor with clinical activity in B-cell malignancies (Friedberg et al., 2010).  
– 7-Azaindole derivatives (compounds 3–7) achieve low-nanomolar potency in co-crystal structures (Singh et al., 2012).

## Other Comments

Oncogenic fusions ITK–SYK (peripheral T-cell lymphoma) and TEL–SYK (myelodysplastic syndrome) drive constitutive signalling (Mócsai et al., 2010). SYK overexpression supports survival of chronic lymphocytic leukaemia and other B-cell cancers (Mócsai et al., 2010). Loss of nuclear SYK correlates with invasive breast cancer and poor prognosis (Mócsai et al., 2010). A gain-of-function variant p.R590Q causes hyper-autophosphorylation, PI3K activation and antibody deficiency with immune dysregulation (Edwards et al., 2025).

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