## Phylogeny

– Tyrosine Kinase (TK) group, SYK/ZAP-70 family as classified by kinome surveys of Manning et al. 2002 (patterson2015arespiratorychain pages 7-7).  
– Single vertebrate paralog: ZAP-70, sharing tandem SH2-kinase architecture (sada2001structureandfunction pages 1-2).  
– Documented orthologs: Gallus gallus, Mus musculus, Rattus norvegicus, Xenopus laevis, Danio rerio, Callorhinchus milii (elephant shark) and Drosophila melanogaster SHARK (patterson2015arespiratorychain pages 7-7).  
– Jawless vertebrate Lj-Syk from Lampetra japonica retains SH2 and kinase domains, indicating early evolutionary origin (liu2015molecularcloningexpression pages 1-2).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosyl-phosphate (sada2001structureandfunction pages 1-2).

## Cofactor Requirements

Catalysis requires Mg²⁺ coordinated by Asp518 within the DFG motif of the active site (atwell2004anovelmode pages 4-5).

## Substrate Specificity

– Peptide-array profiling defines a dominant motif: Pro at −1 and basic Arg/Lys at +2/+3 (-1 P-Y-x-R/K) (yaronbarir2024theintrinsicsubstrate pages 1-2).  
– Acidic or bulky hydrophobic residues (D/E/L/I) tolerated at −1, slight preference for Glu at +1, Pro favoured at +3, and overall exclusion of positively charged residues elsewhere (hobbs2022saturationmutagenesisof pages 6-6).  
– Phosphopriming by pre-existing pY/pT at −1 or +2 further enhances recognition (yaronbarir2024theintrinsicsubstrate pages 16-17).

## Structure

– Domain organisation: N-SH2 (~7-115) – inter-SH2 linker (interdomain A) – C-SH2 (~116-269) – interdomain B (~120 aa) – kinase domain (356-635) (unknownauthors2009autoinhibitionandadapter pages 2-3).  
– Tandem SH2 structure (PDB 1A81) shows head-to-tail binding to diphospho-ITAM peptide (singh2012discoveryanddevelopment pages 4-5).  
– Kinase domain structures: apo 1XBA, Imatinib-bound 1XBB, staurosporine-bound 1XBC; unphosphorylated enzyme adopts active DFG-in, loop-out conformation (atwell2004anovelmode pages 3-4).  
– High-resolution inhibitor complex PDB 4PUZ confirms hydrophobic spine alignment and ordered αC-helix (singh2012discoveryanddevelopment pages 26-27).  
– Key residues: Lys402 (β3), Asp512 (HRD), Asp518 (DFG), activation-loop Tyr525/Tyr526 positioned for autophosphorylation (atwell2004anovelmode pages 4-5).  
– Full-length EM model reveals closed ‘linker-kinase sandwich’ autoinhibition (singh2012discoveryanddevelopment pages 4-5).  
– Imatinib binds SYK in a unique cis orientation exploiting a collapsed ATP pocket, unlike its trans binding to Abl (atwell2004anovelmode pages 3-4).

## Regulation

• Tyrosine phosphorylation  
– ITAM phosphorylation by Lyn/Fyn/Src recruits and activates SYK (tohyama2009proteintyrosinekinase pages 2-2).  
– Y131 autophosphorylation reduces ITAM affinity (unknownauthors2009autoinhibitionandadapter pages 2-3).  
– Y317 phosphorylation creates a C-Cbl docking site and precedes ubiquitination (mocsai2010thesyktyrosine pages 5-6, rao2001thenonreceptortyrosine pages 1-2).  
– Y342/Y346 recruit VAV1 and PI3K-p85 (mocsai2010thesyktyrosine pages 5-6).  
– Y348/Y352 autophosphorylation stabilises the open state; PKCε limits their phosphorylation in human platelets (buitrago2013tyrosinephosphorylationon pages 1-2).  
– Activation-loop Y525/Y526 autophosphorylation completes catalytic activation; SHP-1/PTPN6 and TULA-2 dephosphorylate these sites downstream of GPVI (buitrago2013tyrosinephosphorylationon pages 8-9).  
– C-terminal Y624/Y625 modulate mast-cell signalling (castro2010tyrosinesinthe pages 1-2).  
• Serine phosphorylation  
– PKC phosphorylates S297; PP2A removes this mark. Persistent S297-P suppresses Y525/Y526 phosphorylation and activity (makhoul2020theserinethreonineprotein pages 1-3, makhoul2020theserinethreonineprotein pages 8-10).  
• Ubiquitination  
– C-Cbl mediates antigen-dependent polyubiquitination of active SYK; lysine sites not definitively mapped (paolini2002activationofsyk pages 6-7, buitrago2013tyrosinephosphorylationon pages 8-9).  
• Allosteric control  
– Activation achieved either by SH2-ITAM engagement or linker tyrosine phosphorylation, switching the closed ‘linker-kinase sandwich’ to an open active conformation (‘OR’ logic) (mocsai2010thesyktyrosine pages 3-4).

## Function

– Highly expressed in B cells, early thymocytes, NK cells, mast cells, macrophages, neutrophils, dendritic cells, platelets and osteoclasts; lower levels in several epithelial and fibroblast tissues (mocsai2010thesyktyrosine pages 1-2, singh2012discoveryanddevelopment pages 1-1).  
– Upstream activators: Lyn, Fyn, Src (ITAM phosphorylation); PKC and PP2A modulate serine phosphorylation (tohyama2009proteintyrosinekinase pages 2-2, makhoul2020theserinethreonineprotein pages 8-10).  
– Major substrates/adaptors: BLNK, PLCγ2, LAT, VAV1, PI3K-p85, DEPTOR, LCP2 (sada2001structureandfunction pages 2-3, mocsai2010thesyktyrosine pages 5-6).  
– Central effector in BCR, FcεRI/FcγR, platelet GPVI, C-type lectin and integrin outside-in signalling, controlling Ca²⁺ flux, degranulation, phagocytosis, platelet aggregation and cytokine production (paolini2002activationofsyk pages 2-3, tohyama2009proteintyrosinekinase pages 2-2, antenucci2018phosphorylatedimmunoreceptortyrosinebased pages 12-12).

## Inhibitors

– Imatinib (Gleevec): cis-binding to SYK active site (atwell2004anovelmode pages 3-4).  
– Staurosporine: broad-spectrum ATP-site inhibitor co-crystallised with SYK (atwell2004anovelmode pages 3-4).  
– Fostamatinib disodium (R788; active R406): ATP-competitive inhibitor with clinical activity in non-Hodgkin lymphoma and CLL (friedberg2010inhibitionofsyk pages 8-9).  
– 7-Azaindole chemotypes (e.g., compounds 3–7) achieve low-nanomolar potency in co-crystal structures (singh2012discoveryanddevelopment pages 6-8).

## Other Comments

– Oncogenic fusions: ITK–SYK in peripheral T-cell lymphoma and TEL–SYK in myelodysplastic syndrome drive constitutive signalling (mocsai2010thesyktyrosine pages 12-12, mocsai2010thesyktyrosine pages 16-16).  
– SYK overexpression supports survival of chronic lymphocytic leukemia and other B-cell malignancies (mocsai2010thesyktyrosine pages 16-16).  
– Reduced nuclear SYK correlates with invasive breast cancer and poor prognosis (mocsai2010thesyktyrosine pages 12-12).  
– Gain-of-function variant p.R590Q causes hyper-autophosphorylation, PI3K activation and antibody deficiency with immune dysregulation (edwards2025novelsykvariant pages 4-7).

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