## Phylogeny

• Orthologous genes encoding SH4-U-SH3-SH2-KD-tail kinases have been cloned from Gallus gallus (c-Src), Mus musculus (m-Src), Danio rerio, Drosophila melanogaster and Homo sapiens, demonstrating deep conservation across metazoans (roskoski2004srcprotein–tyrosinekinase pages 1-2, roskoski2004srcprotein–tyrosinekinase pages 9-10).  
• Within the human kinome, SRC belongs to the Tyrosine Kinase (TK) group, Src-family kinases (SFKs); it occupies the SrcA sub-branch that also includes YES1, FYN and FGR, whereas the paralogous SrcB branch comprises HCK, LYN, LCK and BLK (unknownauthors2013diversityinsrcfamily pages 17-22).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosyl-O-phosphate (roskoski2004srcprotein–tyrosinekinase pages 3-5).

## Cofactor Requirements

Catalytic turnover requires a divalent cation, optimally Mg²⁺; Mn²⁺ substitutes in vitro (roskoski2004srcprotein–tyrosinekinase pages 3-5, temps2020preclinicalinvestigationof pages 24-29).

## Substrate Specificity

• Catalytic motif preference: acidic residues at –3/–2, Tyr0, and a hydrophobic residue at +1; canonical peptide EEIYGEF exemplifies this bias (roskoski2004srcprotein–tyrosinekinase pages 8-9).  
• Docking specificity: the SH2 domain preferentially engages pYEEI-type sequences, enhancing processive phosphorylation of substrates bearing this motif (boggon2004structureandregulation pages 2-3).

## Structure

• Linear architecture: N-terminal myristoylated SH4, unique region, SH3, SH2, SH2-kinase linker, bilobed kinase (SH1) domain, C-terminal regulatory tail with Tyr530 (human numbering) (boggon2004structureandregulation pages 1-2, roskoski2004srcprotein–tyrosinekinase pages 2-3).  
• Autoinhibited conformation: SH2 binds pTyr530 and SH3 clamps the proline-rich linker, ejecting helix αC and burying activation-loop Tyr419, thereby rupturing the Lys295–Glu310 ion pair (boggon2004structureandregulation pages 1-2, unknownauthors2013diversityinsrcfamily pages 56-60).  
• Active conformation: tail dephosphorylation or ligand displacement releases SH2/SH3 constraints; Tyr419 autophosphorylation orders the activation loop, realigns αC and completes the hydrophobic spine (cowan­jacob2005thecrystalstructure pages 1-2, unknownauthors2013diversityinsrcfamily pages 87-92).  
• Catalytic landmarks: Lys295 anchors ATP; Asp386 acts as catalytic base; DFG-Asp404 coordinates metal; Trp260 wedges against αC in the off-state (unknownauthors2006selectiveactivationof pages 44-47, unknownauthors2013diversityinsrcfamily pages 87-92).  
• A C-lobe pocket can capture the N-terminal myristate, further stabilizing the closed state (cowan­jacob2005thecrystalstructure pages 1-2).

## Regulation

Post-translational modifications  
– Tyr530 (human) / Tyr527 (chicken) phosphorylation by CSK or CHK enforces SH2-mediated autoinhibition, reducing catalytic efficiency by ~50-fold (boggon2004structureandregulation pages 1-2, roskoski2005srckinaseregulation pages 2-4).  
– Dephosphorylation of pTyr530 by PTP1B, SHP1, SHP2, PTPα or PTPε abolishes this restraint and primes activation (roskoski2005srckinaseregulation pages 7-9, roskoski2005srckinaseregulation pages 11-13).  
– Tyr419 autophosphorylation stabilizes the active conformation and maximizes turnover (cowan­jacob2005thecrystalstructure pages 1-2).  
– Additional sites: Tyr213 (SH2) and Tyr138 (SH3); phosphorylation weakens intramolecular contacts, favouring activation (roskoski2005srckinaseregulation pages 2-4).  
– Ubiquitination of active Src promotes proteasomal degradation, providing negative feedback (taskinen2017earlyemergenceof pages 11-11).

Allosteric and conformational control  
High-affinity external ligands binding SH3 or SH2 can displace intramolecular interactions to activate the kinase independently of tail dephosphorylation (unknownauthors2013diversityinsrcfamily pages 87-92, boggon2004structureandregulation pages 1-2).

Lipid modification  
Gly2 myristoylation is indispensable for membrane anchoring and can dock into the C-lobe pocket of the kinase, contributing to autoinhibition; unlike several SFKs, SRC is not palmitoylated (superti-furga1995structure-functionrelationshipsin pages 1-3, cowan­jacob2005thecrystalstructure pages 1-2).

## Function

• Expression: ubiquitous with highest levels in brain, osteoclasts and platelets (roskoski2004srcprotein–tyrosinekinase pages 2-3).  
• Upstream activators: receptor tyrosine kinases (PDGFR, ERBB family), integrins, immune receptors and certain GPCRs; activation routes include tail dephosphorylation or SH2/SH3 displacement (roskoski2005srckinaseregulation pages 2-4, roskoski2004srcprotein–tyrosinekinase pages 1-2).  
• Major substrates: EGFR Tyr845, focal adhesion kinase (FAK), p190-RhoGAP, CRK-associated substrate (Cas), Vav2, PLCγ1 (haskell2001csrctyrosinephosphorylation pages 2-4, roskoski2005srckinaseregulation pages 7-9).  
• Downstream signalling intersects with Ras and Rho GTPases, STAT transcription factors and osteoclast bone resorption machinery, governing proliferation, adhesion, migration and survival (roskoski2004srcprotein–tyrosinekinase pages 8-9, roskoski2004srcprotein–tyrosinekinase pages 2-3).

## Inhibitors

• Clinically deployed ATP-competitive inhibitors include dasatinib, bosutinib and saracatinib; all occupy the nucleotide pocket and inhibit SFKs with low-nanomolar potency (temps2020preclinicalinvestigationof pages 24-29).  
• Early research probes such as pyrazolo-pyrimidine PP1 and imatinib analogues clarified active-state binding requirements and informed selectivity optimisation (engen2008structureanddynamic pages 1-2, cowan­jacob2005thecrystalstructure pages 1-2).

## Other Comments

• Deletion of the C-terminal tail or Tyr530Phe substitution yields constitutively active, oncogenic enzymes analogous to Rous sarcoma virus v-Src (roskoski2004srcprotein–tyrosinekinase pages 3-5).  
• Src-null mice develop severe osteopetrosis due to defective osteoclast function, underscoring an essential role in bone remodelling (roskoski2004srcprotein–tyrosinekinase pages 2-3).  
• Elevated SRC activity is common in diverse malignancies and correlates with resistance to targeted therapies, cementing its status as a prominent drug target (roskoski2004srcprotein–tyrosinekinase pages 1-2).

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