## Phylogeny

Proto-oncogene tyrosine-protein kinase Src (SRC) belongs to the Src family kinases (SFKs), a conserved group of at least nine non-receptor protein tyrosine kinases (Src, Fyn, Yes, Lck, Lyn, Hck, Blk, Fgr, Yrk) that emerged early in metazoan evolution (Lin, 2005; Ayrapetov, 2006). Sequence-based phylogenetic analyses indicate that SFK diversification paralleled the appearance of increasingly complex receptor systems in multicellular organisms. SRC is closely related to C-terminal Src kinase (Csk) and its homologues, which share a similar domain architecture and antagonize SRC activity (Ayrapetov, 2006; Lin, 2005).

## Reaction Catalyzed

ATP + [protein]-OH(tyrosine) ⇌ ADP + [protein]-O-PO₃²⁻(phosphotyrosine) + H⁺ (Ayrapetov, 2006; Lin, 2005).

## Cofactor Requirements

Mg²⁺ is required to coordinate ATP in the active site and enable phosphotransfer (Ayrapetov, 2006; Lin, 2005).

## Substrate Specificity

SRC phosphorylates tyrosine residues and selects substrates through its catalytic domain together with SH2 and SH3 modules.  
• SH2 domain: high affinity for phosphotyrosine motifs, especially pYEEI; the autoinhibitory intramolecular contact employs a non-canonical pTyr-Gln-Pro-Gly sequence (Ayrapetov, 2006).  
• SH3 domain: binds proline-rich regions in substrates, providing an additional layer of targeting (Korade-Mirnics & Corey, 2000; Ayrapetov, 2006).  
Dual engagement by SH2/SH3 domains refines substrate selection and sub-cellular localization.

## Structure

SRC is a modular kinase comprising:  
1. SH4 domain with an N-terminal myristoylation signal for membrane anchoring (Schenone et al., 2007; Ayrapetov, 2006).  
2. Unique region (poorly conserved) that mediates specific protein interactions.  
3. SH3 domain (proline-rich peptide binder).  
4. SH2 domain (phosphotyrosine binder).  
5. SH1 catalytic (kinase) domain with the canonical bilobed fold; autophosphorylation on Tyr416 (human Tyr419) in the activation loop maximizes catalytic activity, whereas phosphorylation of the C-terminal tail residue Tyr527 (human Tyr530) promotes intramolecular SH2 binding and maintains the inactive conformation (Ayrapetov, 2006).  
Proper positioning of the αC-helix and a hydrophobic spine stabilize the active state once autoinhibition is relieved (Ayrapetov, 2006; Schenone et al., 2007).

## Regulation

• Inactivation: C-terminal phosphorylation on Tyr527/Tyr530 by Csk or Chk locks SRC in a closed conformation via SH2-tail binding; the SH3 domain concurrently interacts with a proline-rich internal linker (Ayrapetov, 2006).  
• Activation: Dephosphorylation of the C-terminal tyrosine permits an open conformation, followed by autophosphorylation of Tyr416/Tyr419 in the activation loop to achieve full activity (Ayrapetov, 2006; Lin, 2005).  
• Additional control: SH3-linker contacts (e.g., Trp260) reinforce autoinhibition, while N-terminal myristoylation targets SRC to membranes where receptor engagement facilitates activation (Ayrapetov, 2006; Schenone et al., 2007).

## Function

SRC is rapidly activated downstream of diverse receptors (immune receptors, integrins, receptor tyrosine kinases, GPCRs, and cytokine receptors) and phosphorylates substrates that regulate gene transcription, cell adhesion, cell-cycle progression, apoptosis, and migration (Ayrapetov, 2006; Sato, 2013; Korade-Mirnics & Corey, 2000).  
• Example substrates: EGFR Tyr845 (mitogenic signaling) and focal adhesion kinase (FAK) during integrin-mediated adhesion and motility (Schenone et al., 2007; Korade-Mirnics & Corey, 2000).  
Through its broad substrate range, SRC serves as a signaling hub influencing cytoskeletal remodeling, survival, and proliferation.

## Inhibitors

Numerous ATP-competitive small molecules, including PP1 and PP2, bind the SRC ATP pocket and inhibit kinase activity; these compounds are under investigation for anti-angiogenic and anti-tumor applications (Schenone et al., 2007).

## Other Comments

Hyperactivation or overexpression of SRC is linked to several cancers (breast, colon, pancreatic, lung, and hematological malignancies), making SRC a prominent therapeutic target. Selectivity and toxicity remain challenges because of kinase domain conservation. Strategies under exploration include structure-guided design and allosteric inhibitors, as well as modulation of negative regulators such as Csk/Chk (Sato, 2013; Schenone et al., 2007; Ayrapetov, 2006).

## References

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