1. Phylogeny  
   Proto‐oncogene tyrosine‐protein kinase Src (commonly referred to as c‐Src or pp60c‐Src) is a founding member of the Src family kinases (SFKs), a conserved group of non‐receptor tyrosine kinases present from unicellular organisms to mammals (alvarez2006theroleof pages 1-2). Src is found in all metazoans, with orthologs identified in invertebrates and vertebrates, and its evolution reflects a diversification of regulatory mechanisms that parallel the emergence of multicellularity (mizenina2000kinasesofthe pages 2-4, parsons2004srcfamilykinases pages 3-4). As part of the kinome, Src is assigned to a subgroup of cytoplasmic tyrosine kinases where its modular architecture is maintained by highly conserved regulatory and catalytic domains; this group evolved alongside other non‐receptor protein kinases with similar domain organizations (shah2018thesrcmodule pages 19-20).
2. Reaction Catalyzed  
   Src catalyzes the transfer of the terminal phosphate group from ATP to specific tyrosine residues on protein substrates. In this reaction, ATP and a substrate protein containing an accessible tyrosine hydroxyl group produce ADP and a phosphotyrosine‐modified protein, thereby modulating the function of targeted proteins via post‐translational modification (frame2002srcincancer pages 2-4, shah2018thesrcmodule pages 27-28).
3. Cofactor Requirements  
   The catalytic activity of Src requires the presence of divalent metal ions, with Mg²⁺ being the essential cofactor. Magnesium ions coordinate with ATP to facilitate the proper positioning of the phosphate groups within the active site, ensuring efficient phosphoryl transfer during the kinase reaction (mizenina2000kinasesofthe pages 2-4, parsons2004srcfamilykinases pages 3-4).
4. Substrate Specificity  
   Src exhibits substrate specificity for tyrosine residues within its target proteins, with its recognition largely influenced by interactions mediated by its SH2 and SH3 domains. The kinase shows affinity for substrates associated with cell adhesion and cytoskeletal reorganization—including focal adhesion proteins such as focal adhesion kinase (FAK) and paxillin, as well as components of cell–cell junctions—and phosphorylates these substrates on specific tyrosine residues to regulate downstream signaling events (alvarez2006theroleof pages 2-4, frame2002srcincancer pages 2-4, parsons2004srcfamilykinases pages 3-4). Although a strict consensus motif has not been universally defined for Src, its substrate specificity is a function of both the catalytic domain’s inherent preference for tyrosine residues and the spatial-temporal recruitment of substrates via its regulatory domains (puchetamartinez2016anallostericcrosstalk pages 6-7).
5. Structure  
   Src is composed of several distinct domains that each contribute to its catalytic activity and regulation. Its N-terminal region contains a myristoylation signal that directs membrane association, which is essential for its proper subcellular localization (alvarez2006theroleof pages 1-2, mizenina2000kinasesofthe pages 2-4). This is followed by a unique domain that, while less conserved, contributes to the specificity of protein–protein interactions. Adjacent to this is the SH3 domain, which binds proline-rich sequences present in target or regulatory proteins, and the SH2 domain, which specifically recognizes phosphotyrosine motifs; both domains are critical for substrate selection and intramolecular interactions that maintain Src in its autoinhibited conformation (alvarez2006theroleof pages 2-4, berndt2021newstructuralperspectives pages 9-11). The central catalytic domain, also termed the kinase domain or SH1, features a bilobal structure with a smaller N-terminal lobe and a larger C-terminal lobe. Key structural elements include the activation loop—which contains the critical autophosphorylation site at Tyr416 that stabilizes the active conformation—the DFG motif and the αC-helix, as well as hydrophobic spines that contribute to the integrity of the active site (berndt2021newstructuralperspectives pages 9-11, mizenina2000kinasesofthe pages 2-4). The C-terminal tail contains a regulatory tyrosine residue (Tyr527 in human c-Src numbering) whose phosphorylation by kinases such as CSK enforces an intramolecular inhibitory interaction with the SH2 domain, thereby locking Src in a closed, inactive conformation (alvarez2006theroleof pages 1-2, mizenina2000kinasesofthe pages 5-7).
6. Regulation  
   Regulation of Src activity is achieved through a combination of phosphorylation events, intramolecular domain interactions, and allosteric modulation. In its inactive state, Src is maintained in an autoinhibited conformation by the binding of the phosphorylated C-terminal tyrosine (Tyr527) to its own SH2 domain, with the SH3 domain engaging a polyproline motif in the linker region; this conformational arrangement restricts access to the catalytic site (alvarez2006theroleof pages 1-2, mizenina2000kinasesofthe pages 4-5). Activation of Src requires dephosphorylation of Tyr527, which disrupts these inhibitory interactions, and subsequent autophosphorylation at Tyr416 within the activation loop, a process critically dependent on intermolecular interactions and conformational flexibility (alvarez2006theroleof pages 2-4, berndt2021newstructuralperspectives pages 8-9). In addition, regulatory mechanisms include allosteric control through binding of SH2 and SH3 ligands, which can displace the intramolecular contacts and promote kinase activation (puchetamartinez2016anallostericcrosstalk pages 6-7, parsons2004srcfamilykinases pages 3-4). Src activity can also be modulated by redox mechanisms, whereby oxidation of specific cysteine residues alters its conformation and catalytic efficiency (giannoni2014redoxcircuitriesdriving pages 20-23). External signals from receptor tyrosine kinases, immune receptors, integrins, and G protein-coupled receptors result in receptor clustering and recruitment of Src to dynamic plasma membrane complexes, further influencing its activation state (alvarez2006theroleof pages 9-10, suga2018srcsignalingin pages 1-2).
7. Function  
   Src plays a central role in the transduction of signals emanating from a wide array of cellular receptors, including immune response receptors, integrins, receptor protein tyrosine kinases, G protein-coupled receptors, and cytokine receptors (alvarez2006theroleof pages 1-2). Upon receptor engagement, Src is recruited to the receptor complexes where it phosphorylates specific tyrosine residues on the receptors themselves as well as on downstream adaptor and effector proteins. This phosphorylation event initiates and amplifies signaling cascades that regulate diverse biological activities such as gene transcription, cell adhesion, cytoskeletal organization, cell cycle progression, apoptosis, migration, and cellular transformation (alvarez2006theroleof pages 2-4, berndt2021newstructuralperspectives pages 8-9). In the context of cell adhesion, Src phosphorylates substrates such as focal adhesion kinase (FAK) and paxillin, thereby modulating focal adhesion turnover and actin cytoskeletal dynamics, which are critical for cell migration and the formation of specialized cell–cell junctions including adherens and gap junctions (frame2002srcincancer pages 2-4, byeon2012theroleof pages 1-2). Src is further implicated in the regulation of pre-mRNA processing through phosphorylation of RNA-binding proteins, and it influences receptor internalization processes via phosphorylation of clathrin heavy chain (alvarez2006theroleof pages 4-5). In osteoclasts, Src is essential for bone resorption; its interaction with PTK2B/PYK2 and subsequent phosphorylation of downstream targets such as CBL leads to the recruitment of phosphatidylinositol 3-kinase, a critical step for osteoclast function (alvarez2006theroleof pages 8-9). Moreover, Src has been shown to participate in antiviral signaling, modulate signaling cascades downstream of epidermal growth factor receptor (EGFR), and affect gap junction communication by phosphorylating connexin-43, thereby underscoring its multifaceted role in cellular regulation (alvarez2006theroleof pages 8-9, giannoni2014redoxcircuitriesdriving pages 1-4).
8. Other Comments  
   Src has been the target of extensive therapeutic research due to its involvement in oncogenesis and other diseases. Inhibition of Src activity using small-molecule inhibitors such as dasatinib and bosutinib has been explored in various clinical contexts, particularly in malignancies where aberrant Src activation contributes to tumor progression and metastasis (alvarez2006theroleof pages 8-9, puls2011currentstatusof pages 10-11). Src’s overexpression and deregulated kinase activity have been documented in a range of solid tumors, including breast, colon, pancreatic cancers, and hematologic malignancies, making its regulation a critical area of interest for targeted therapy (frame2002srcincancer pages 11-12, puls2011currentstatusof pages 11-11). Mutations and alterations that affect regulatory phosphorylation sites, such as those involving the C-terminal regulatory tyrosine or residues within the activation loop, are known to disrupt the delicate balance of Src regulation and promote oncogenic transformation (mizenina2000kinasesofthe pages 5-7, shah2018thesrcmodule pages 27-28). Additionally, redox regulation and post-translational modifications contribute to the complexity of Src’s function, and ongoing research continues to elucidate mechanisms that may be exploited for more selective therapeutic interventions (giannoni2014redoxcircuitriesdriving pages 20-23, byeon2012theroleof pages 11-13).
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