1. Phylogeny  
   Proto‐oncogene tyrosine‐protein kinase Src is a member of the non‐receptor protein tyrosine kinase family known as the Src family kinases (SFKs), which are found in all metazoans and can be traced back to early unicellular holozoans. Src displays a high degree of conservation across species, with well‐characterized orthologs in species such as chicken (where Tyr527 was first described), mouse, and human, consistent with its inclusion in the evolutionary core set of protein kinases that emerged prior to multicellularity (sicheri1997structuresofsrcfamily pages 1-2, brickell1991thecsrcfamily pages 1-3, taskinen2017earlyemergenceof pages 1-2). Within the human kinome, Src is classified in a subgroup of cytoplasmic tyrosine kinases that is distinct from receptor tyrosine kinases and is evolutionarily related to other SFKs such as Fyn, Yes, Lyn, Lck, Hck, and others (sicheri1997structuresofsrcfamily pages 1-2, taskinen2017earlyemergenceof pages 1-2). The pioneering studies by Manning and colleagues have documented the evolutionary conservation and diversification of these kinases from yeast to man, establishing their phylogenetic context within a broad family of regulatory enzymes (Manning et al. 2002, Manning et al. 2002).
2. Reaction Catalyzed  
   Src catalyzes the transfer of the γ‐phosphate from adenosine triphosphate (ATP) to specific tyrosine residues on substrate proteins, thereby converting ATP into adenosine diphosphate (ADP) and phosphorylating the target protein on a tyrosine residue. In chemical terms, the reaction can be represented as:  
   ATP + [protein]–tyrosine → ADP + [protein]–phosphotyrosine + H⁺ (template adapted).
3. Cofactor Requirements  
   The catalytic activity of Src is dependent on the presence of divalent metal ions, most commonly magnesium (Mg²⁺), which is required to coordinate the binding of ATP in the active site. Mg²⁺ functions as a cofactor that facilitates proper ATP orientation for effective phosphotransfer (roskoski2004srcprotein–tyrosinekinase pages 1-2, roskoski2004srcprotein–tyrosinekinase pages 2-3).
4. Substrate Specificity  
   Src exhibits intrinsic substrate specificity as a tyrosine kinase. Recent investigations into the intrinsic substrate specificity of the human tyrosine kinome indicate that Src preferentially phosphorylates substrates that contain a recognition motif characterized by a central tyrosine flanked by acidic and hydrophobic residues. For example, a consensus motif may involve a pattern in which the target tyrosine is preceded by hydrophobic residues and followed by acidic amino acids, defining the recognition sequence that facilitates substrate binding (Yaron-Barir2024 pages 1174-1181). This substrate preference allows Src to phosphorylate a wide range of substrates involved in adhesion, migration, and signal transduction—including cytoskeletal proteins and focal adhesion components—thus integrating a diverse array of cellular responses (alcala2020targetingsrckinase pages 19-21).
5. Structure  
   Src is organized into several distinct structural domains that work cooperatively to regulate its activity. At the extreme N-terminus, the SH4 domain contains a myristoylation signal that facilitates membrane localization. Adjacent to the SH4 domain is a Variable (Unique) region that confers isoform-specific functions. This is followed sequentially by the SH3 and SH2 domains; the SH3 domain recognizes proline-rich sequences, whereas the SH2 domain binds to phosphotyrosine-containing motifs, and both domains also contribute to autoinhibition by interacting intramolecularly with other regions of the protein. The central catalytic domain (often referred to as the SH1 or kinase domain) contains an activation loop that includes a key tyrosine residue (Tyr416 in chicken Src, with minor numbering differences in human Src) whose phosphorylation is associated with full activation, and possesses a conserved C-helix that is critical for proper catalytic alignment. Finally, a C-terminal tail contains the regulatory tyrosine residue (Tyr527 in chicken Src) whose phosphorylation by C-terminal Src kinase (Csk) promotes the inactive conformation by binding the SH2 domain (roskoski2004srcprotein–tyrosinekinase pages 5-7, sicheri1997structuresofsrcfamily pages 1-2). These structurally defined modules collectively enable Src to adopt distinct conformations ranging from an autoinhibited state to a catalytically active state (shah2018thesrcmodule pages 1-3).
6. Regulation  
   The regulation of Src involves multiple layers of control. A key mechanism is phosphorylation‐dependent conformational change: autophosphorylation within the activation loop (typically at Tyr416) stabilizes the active conformation, while phosphorylation at the C-terminal regulatory tyrosine (Tyr527) by Csk enforces an inactive conformation by promoting intramolecular binding of the SH2 domain (chong2005endogenousandsynthetic pages 1-2, roskoski2004srcprotein–tyrosinekinase pages 9-10). Additional post-translational modifications include acetylation, ubiquitination, SUMOylation, and oxidation, which collectively modulate Src’s cellular localization, stability, and kinase activity. For instance, lipid modifications such as myristoylation at the N-terminus are essential for proper membrane targeting, while reactive oxygen species have been reported to alter Src activity through reversible oxidation (min2022crosstalkbetweenwnt pages 23-24). Moreover, regulatory proteins such as protein tyrosine phosphatases (for example, RPTPα) are responsible for dephosphorylating key regulatory residues and thus contribute to the dynamic control of Src activity. The conformational balance between its inactive (closed) and active (open) states is maintained by these combined phosphorylation events and interdomain interactions (roskoski2004srcprotein–tyrosinekinase pages 8-9, chong2005cterminalsrckinase pages 1-2).
7. Function  
   Src plays an integral role in transducing a variety of extracellular signals into appropriate intracellular responses. Upon activation by receptor clustering or dimerization at the plasma membrane—including engagement of immune receptors, integrins, receptor tyrosine kinases, G protein‐coupled receptors, and cytokine receptors—Src is recruited to receptor complexes where it phosphorylates intracellular substrates. These substrates include cytoskeletal regulatory proteins such as AFAP1 and cortactin, focal adhesion components such as focal adhesion kinase (PTK2/FAK) and paxillin, and junctional proteins like beta-catenin, thereby modulating cytoskeletal organization, cell adhesion, and migration (alcala2020targetingsrckinase pages 19-21, correlative details from Information section). Src also influences gene transcription and cell cycle progression by phosphorylating RNA-binding proteins and components of mitogen-activated signaling pathways, including those activated by PDGF and EGF. In addition, Src has been implicated in the Ras pathway via phosphorylation of regulators such as RASA1 and RASGRF1, and in receptor internalization through phosphorylation of clathrin heavy chain, thereby linking it to endocytic mechanisms. Src-mediated phosphorylation events contribute to key biological processes such as immune responses, osteoclast function in bone resorption, and even antiviral signaling via modulation of RIG-I pathways. This broad substrate repertoire and its central position at the hub of multiple signaling networks underscore the critical role of Src as a primary kinase activated by numerous receptors, facilitating further activation of downstream protein tyrosine kinase families (alcala2020targetingsrckinase pages 19-21, jin2020regulationofsrc pages 1-3).
8. Other Comments  
   A number of small-molecule inhibitors have been developed to target Src kinase activity, with compounds such as dasatinib and BMS-354825 demonstrating potent, selective antitumor activity in preclinical models. The clinical relevance of Src is highlighted by its frequent overexpression and hyperactivation in various human cancers including breast, colorectal, pancreatic, and ovarian carcinomas. Given the functional redundancy among SFKs, the development of Src inhibitors is of particular interest for personalized cancer therapy and for overcoming therapy resistance. In addition, disease-associated mutations and post-translational dysregulations have been reported to enhance Src kinase activity, which can promote oncogenesis by deregulating cell adhesion, migration, and proliferation (jin2020regulationofsrc pages 15-17, chong2005cterminalsrckinase pages 2-3). The complexity of Src regulation—encompassing phosphorylation dynamics, protein-protein interactions mediated by its SH2 and SH3 domains, and other modifications such as ubiquitination—provides multiple targets for pharmacological intervention. Furthermore, ongoing research continues to refine our understanding of its intrinsic substrate specificity, as detailed in recent high-resolution studies of the human tyrosine kinome (Yaron-Barir2024 pages 1174-1181).
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