

## Src

## Key References

- Abram, C.L., et al., Src family tyrosine kinases and growth factor signaling., *Exp. Cell. Res.*, **254**, 1-13 (2000).
- Boggon, T.J., et al., Structure and regulation of Src family kinases., *Oncogene*, **23**, 7918-7927 (2004).
- Bromann, P.A., et al., The interplay between Src family kinases and receptor tyrosine kinases., *Oncogene*, **23**, 7957-7968 (2004).
- Cole, P.A., et al., Protein tyrosine kinases Src and Csk: a tail's tale., *Curr. Opin. Chem. Biol.*, **7**, 580-585 (2003).
- Frame, M.C., Src in cancer: deregulation and consequences for cell behavior., *Biochim. Biophys. Acta.*, **1602**, 114-130 (2002).
- Kalia, L.V., et al., Src in synaptic transmission and plasticity., *Oncogene*, **23**, 8007-8016 (2004).
- Luttrell, D.K., et al., Not so strange bedfellows: G-protein-coupled receptors and Src family kinases., *Oncogene*, **23**, 7969-7978 (2004).
- Palacios, E.H., et al., Function of the Src-family kinases, Lck and Fyn, in T-cell development and activation., *Oncogene*, **23**, 7990-8000 (2004).
- Playford, M.P., et al., The interplay between Src and integrins in normal and tumor biology., *Oncogene*, **23**, 7928-7946 (2004).
- Serfas, M.S., et al., Brk, Srm, Frk, and Src42A form a distinct family of intracellular Src-like tyrosine kinases., *Oncol. Res.*, **13**, 409-419 (2003).
- Shupnik, M.A., Crosstalk between steroid receptors and the c-Src-receptor tyrosine kinase pathways: implications for cell proliferation., *Oncogene*, **23**, 7979-7989 (2004).
- Thomas, S.M., et al., Cellular functions regulated by Src family kinases., *Annu. Rev. Cell Dev. Biol.*, **13**, 513-609 (1997).

## Overview

Since the isolation of v-Src as the transforming component of Rous sarcoma virus, and the subsequent identification of its cellular homolog c-Src, there has been intense interest in its activity and regulation. Src is the founding member of a group of non-receptor protein tyrosine kinases termed the Src family kinases (SFKs). All members share a basic multidomain structure and a high degree of homology. SFKs can be further subdivided into a core group of "typical" SFKs which in humans consists of eight members (Src, Blk, Fgr, Fyn, Hck, Lck, Lyn, and Yes), a small group of "atypical" members (Brk, Frk and Srm), and two closely related kinases (Csk and Matk), that regulate the typical SFKs.

Typical SFKs are defined by the presence of five domains: a unique region of variable length, containing at its extreme amino-terminus motifs specifying modification by the short fatty acids palmitate and/or myristate; an SH3 domain, which mediates binding to specific PXXP motifs; an SH2 domain which governs binding to specific phosphotyrosine residues; a catalytic domain containing a tyrosine in the activation loop whose phosphorylation modulates catalytic activity; and a short carboxy-terminal tail with a tyrosine residue whose phosphorylation negatively regulates the enzyme. The atypical members all share a similar core structure, although none have the motif required for myristylation, and while Frk and Brk have a regulatory tyrosine in the C-tail, Srm does not. In addition, all atypical members have a nuclear localization sequence in the SH2 domain. The regulators Csk and Matk lack myristylation motifs, activation loop tyrosines and C-terminal regulatory tails.

The activity of typical SFKs is exquisitely regulated by structural constraints. They

are usually held in a "closed" inactive form, and transition to an "open" active conformation upon a stimulus. For example Src in the inactive form is phosphorylated in the C-terminal tail (tyrosine 530), a reaction usually carried out by Csk. This phosphorylation favors interaction between the tail and the SH2 domain which, together with a second intramolecular interaction between the SH3 domain and sequences linking the SH2 domain and the kinase domain, promotes the closed conformation. The SH2 and SH3 domains are masked, and the conformation of the kinase domain is unfavorable for catalysis. Transition to the active state can occur via either dephosphorylation of the tail tyrosine or by the binding of high affinity ligands to the SH2 and/or SH3 domains.

SFKs are frequently activated when extracellular ligands associate with their cognate receptors (such as receptor tyrosine kinases, G protein-coupled receptors, integrin receptors and immune recognition receptors) as well as intrinsically during mitosis. SFKs participate in mitogenesis, cell survival, cytoskeletal reorganization and motility, as well as specialized functions such as immune cell development, neuronal cell signaling, osteoclast and platelet function etc. In addition, deregulation and/or overexpression of both typical and atypical SFKs have been implicated in cancer causation. In keeping with the involvement of SFKs in many signaling pathways, a large and growing number of SFK substrates are being identified (currently more than 50 for Src alone).

Several small molecule inhibitors of SFKs have been identified, including (PP2 and SU6656) displays considerable selectivity for SFKs and can inhibit Lck and Fyn in the

nanomolar range; however it is an equally potent inhibitor of the PDGF receptor and other RTKs, as well as Tec kinases. SU6656 inhibits SFKs in the high nanomolar range, and does not inhibit the PDGF receptor or Tec, but it is very unlikely to be totally selective for SFKs. Where possible, results obtained with an SFK should be confirmed with a second inhibitor, or using other means.

# Src

<b>FAMILY MEMBERS</b>	Src	Blk	Fgr	Fyn	Hck	Lck	Lyn	Yes
<b>OTHER NAMES</b>	c-Src, pp60 <sup>c-Src</sup>	Not found	Src2 p55 <sup>c-f9r</sup>	p59 <sup>Fyn</sup> Slk/Syn	JTK9	Not found	JTK8	c-yes p61 <sup>yes</sup>
<b>MOLECULAR WEIGHT/</b>	59.8 kDa	57.7 kDa	59.4 kDa	60.7 kDa	57.3 kDa	58.0 kDa	58.5 kDa	60.8 kDa
<b>AMINO ACIDS</b>	536	505	529	537	526	509	512 (Lyna) 491 (Lynb)	543
<b>ISOFORMS</b>	nSrc	Not known	Not known	Fyna Fynb Fync	p59 <sup>Hck</sup> p61 <sup>Hck</sup>	Not known	Lyna Lynb	Not known
<b>SPECIES</b>	Avian (v-Src), human, monkey, mouse, <i>Xenopus</i> , rat, chordite	Human, mouse, rat	Human, mouse, rat	Human, mouse, rat, <i>Xenopus</i>	Human, monkey, mouse, rat	Human, monkey, mouse, rat	Human, monkey, mouse, rat	Avian (v-Yes) human, monkey, mouse, rat, fish, <i>Xenopus</i>
<b>DOMAIN ORGANIZATION</b>	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase
<b>PHOSPHORYLATION SITES</b>	Ser <sup>12</sup> , Ser <sup>17</sup> , Tyr <sup>216</sup> , Tyr <sup>419</sup> , Tyr <sup>530</sup>	Tyr <sup>389</sup> , Tyr <sup>501</sup>	Tyr <sup>523</sup> , Tyr <sup>412</sup>	Tyr <sup>531</sup> , Tyr <sup>420</sup>	Tyr <sup>522</sup> , Tyr <sup>390</sup>	Tyr <sup>505</sup> , Tyr <sup>394</sup>	Tyr <sup>508</sup> , Tyr <sup>397</sup>	Tyr <sup>537</sup> , Tyr <sup>426</sup>
<b>TISSUE EXPRESSION</b>	Ubiquitous	B cells	Myeloid cells B cells	Ubiquitous cells	Myeloid cells	T cells	Myeloid cells B	Ubiquitous
<b>SUBCELLULAR ORGANIZATION</b>	Cytoplasm, plasma membrane	Cytoplasm	Cytoplasm	Cytoplasm, plasma membrane	Cytoplasm, plasma membrane	Plasma membrane	Cytoplasmic membrane and cytoplasm (endocytic vesicles and coated pits)	Cytoplasmic membrane
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	ADAM12, Csk, EGFR, FKHR, Sam68, Paxillin, WASp, 14-3-3 β/γ/ε, PKCε/ζ	Bcl2, CBL, PLCγ2, ubiquitin protein ligase E3A	CCR3, CD24, SLAM, SHIP, WASp	PI3K (p85α), Fyn-binding protein, SLAM, SAP, Paxillin	WIP, Abl, p130Cas	ADAM15, p130Cas Cbl, Fas receptor, Jak3, Sam68, PI3K, SHP1	Jak2, Shc, Slp-76	YAP, occludins, CD36, kAK2, PP2A, PyK2, p120GAP
<b>UPSTREAM ACTIVATORS</b>	ErbB1, AP-1, PDGFR, IR, AMPK, Neu, fibronectin, FGR, VDR, PI3K/Akt/eNOS pathway, LPS, IFNγ	AML1, BSAP/PAX5, NERF/ELF-2, NFκB, BSAP, EBF, antigen receptor complex	Negative regulator of PP1a, chemokine signaling, PMN adhesion, urokinase	CD95L, NSAIDs, RAFTK, FAK, Vav, PDGFR	Actin	CD4, CD8	Integrin (αIIb β3)	LTB4, Et-1, PDGFR, CSF1R, Neu, FGR, GM-CSF

## FOOTNOTES

## Src

<b>DOWNSTREAM ACTIVATION</b>	EGFR, Shc, dynamin, clathrin, Raf-1, JAK1, STAT1/3/5, Tks5, G protein-linked receptor kinase 2, caveolin-1	Not known	PI3K, p120/130, Cbl, Pyk2, p190RhoGAP, Rac	PI3K, p120/130, Cbl, Pyk2	Ca <sup>2+</sup> , MAPK	p56dok, p62dok, Zap-70, PLCγ1, NFAT	Btk, Syk, Cbl, PI3K (p85α),	PyK2, CD46,
<b>ACTIVATORS</b>	Growth factors	Not known	Not known	Not known	Not known	Not known	Not known	Not known
<b>INHIBITORS</b>	PP1, PP2, SU6656	Not known	Not known	PP1, PP2, SU6656	PP1, PP2	PP1, PP2	Not known	PP1, PP2, SU6656
<b>PHYSIOLOGICAL FUNCTION</b>	Cellular proliferation and differentiation, bone remodelling	B lymphoid cell signal transduction	Cellular migration and adhesion	Synaptic plasticity, implicated in learning and memory, cellular growth	May contribute to neutrophil migration and may regulate the degranulation process of neutrophils	T-Cell activation	Mast cell adhesion	Neutrophil degranulation, cellular proliferation, cell-cell interactions
<b>DISEASE RELEVANCE</b>	Embryonic development, multiple cancers, osteoporosis	Some leukemias	B-cell acute lymphoblastic leukemia	Neurological disease impaired special learning	B-cell acute lymphoblastic leukemia	Some leukemias	Glomerulonephritis, IgM hyperglobulinemia	Colon carcinomas, hematopoietic disorders

## FOOTNOTES

# Src

<b>FAMILY MEMBERS</b>	Csk	Matk	Brk	Srm	Frk
<b>OTHER NAMES</b>	—	Chk, Ctk, Hyl	Ptk6	Srms: Src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristylation sites	Rak, Gtk (rat), lyk (mouse)
<b>MOLECULAR WEIGHT</b>	50.7 kDa	56.5 kDa	51.8 kDa	54.8 kDa	58.3 kDa
<b>AMINO ACIDS</b>	450	507	451	488	505
<b>ISOFORMS</b>	Not known	Matka Matkb	Not known	Not known	Not known
<b>SPECIES</b>	Human, monkey, mouse, rat	Human, monkey, mouse, rat	Human, monkey, mouse, rat	Human, monkey, mouse, rat, avian	Human, monkey, mouse, rat
<b>DOMAIN ORGANIZATION</b>	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase	SH3-SH2-Tyr kinase
<b>PHOSPHORYLATION SITES</b>	Not known	Not known	Tyr <sup>342</sup> , Tyr <sup>447</sup>	Tyr <sup>380</sup>	Tyr <sup>387</sup> , Tyr <sup>497</sup>
<b>TISSUE EXPRESSION</b>	Ubiquitous	Hematopoietic, brain	Predominantly epithelial	Predominantly epithelial	Predominantly epithelial
<b>SUBCELLULAR ORGANIZATION</b>	Cytoplasmic membrane	Cytoplasmic	Cytoplasmic, nucleus	Cytoplasmic membrane, nucleus	Nuclear, perinuclear
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	Fyn, Cbl, IGF-1R, Src	PyK2, Paxillin, HER2/Neu, c-Kit	Sam68, Slm1	Not known	pRb
<b>UPSTREAM ACTIVATORS</b>	H <sub>2</sub> O <sub>2</sub>	Thrombin	EGF	Not known	Not known
<b>DOWNSTREAM ACTIVATION</b>	Not known	Not known	STAP2/BKS, Rac1, paxillin, Sam68	Not known	Not known
<b>ACTIVATORS</b>	PP1, PP2	Not known	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Negative regulators of SFK	Negative regulators of SFK, hematopoietic cell signal transduction, inhibitory role in T cell proliferation	May function as an intracellular signal transducer in epithelial tissue, cell migration	Not known	Regulation of cellular growth
<b>DISEASE RELEVANCE</b>	Colorectal cancer	Possible role in breast cancer	Possible role in breast cancer	Not known	Possible role in breast cancer and acute myelogenous leukemia

## FOOTNOTES

## Src

<b>FAMILY MEMBERS</b>	MST1	YSK1	HGK
<b>OTHER NAMES</b>	Krs-2	SOK	NIK
<b>GROUP</b>	GCK-II	GCK-III	GCK-IV
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	56 kDa 487 aa	48 kDa 426 aa	142 kDa 1239 aa
<b>ISOFORMS</b>	MST1, MST2	YSK1, MST3, MASK	HGK, TNIK, MINK
<b>SPECIES</b>	Human	Human	Human
<b>DOMAIN ORGANIZATION</b>	N-terminal kinase domain, dimerization domain, inhibitory domain	N-terminal kinase domain	N-terminal kinase domain, coiled-coil domain, CNH domain
<b>PHOSPHORYLATION SITES</b>	Thr <sup>183</sup> Thr <sup>187</sup>	Thr <sup>174</sup> Thr <sup>191</sup>	Thr <sup>187</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Ubiquitous	Brain, testis
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic, nuclear	Golgi apparatus	
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	NORE, DAP4	GM130	Nck, STAT3, MEK1 (M6939)
<b>UPSTREAM ACTIVATORS</b>	UV, taxol, caspases (C5482, C6607, C2854, C1224, C6357, C6482, C4974, C2978, C8726)	Oxidant stress, GM130	EphR
<b>DOWNSTREAM ACTIVATION</b>	H2B	14-3-3 $\zeta$	STAT3
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Apoptosis	Cell migration transformation	Cell migration
<b>DISEASE RELEVANCE</b>	Not known	Not known	Tumorigenesis

## FOOTNOTES

## Src

<b>FAMILY MEMBERS</b>	LOK	OSR1	MYO3A
<b>OTHER NAMES</b>	Stk10; lymphocyte-oriented kinase protein 1	Oxysterol-binding protein-related	Myosin IIIa
<b>GROUP</b>	GCK-V	GCK-VI	GCK-VII
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	130 kDa 58 kDa 968 aa 527 aa	185 kDa 1616 aa	Not known
<b>ISOFORMS</b>	LOK, SLK OSR1, SPAK	MYO3A, SNICK	Not known
<b>SPECIES</b>	Human	Human	Human
<b>DOMAIN ORGANIZATION</b>	N-terminal kinase domain, coiled-coil domain	N-terminal kinase domain, PF1/PF2 domains	N-terminal kinase domain, IQ motifs
<b>PHOSPHORYLATION SITES</b>	Ser <sup>438</sup>	Ser <sup>339</sup>	Ser <sup>1355</sup>
<b>TISSUE DISTRIBUTION</b>	Spleen, thymus, bone marrow	Ubiquitous	Retina, brain, testis
<b>SUBCELLULAR LOCALIZATION</b>	Not known	Cytosolic, nuclear	Cytoskeleton
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	Plk1	PAK1, NKCC 1/2	Calmodulin ( <b>P2277</b> ), actin ( <b>A9718</b> )
<b>UPSTREAM ACTIVATORS</b>	Not known	Sorbitol ( <b>S3755</b> )	Not known
<b>DOWNSTREAM ACTIVATION</b>	Plk1, H2A PAK1	MBP ( <b>M1891</b> )	Not known
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Cell adhesion, cell cycle	Not known	Morphogenesis of photoreceptors
<b>DISEASE RELEVANCE</b>	Not known	Not known	Progressive, nonsyndromic hearing loss

## FOOTNOTES

## Src

<b>FAMILY MEMBERS</b>	TAO2
<b>OTHER NAMES</b>	PSK
<b>GROUP</b>	GCK-VIII
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	138 kDa 1235 aa
<b>ISOFORMS</b>	TAO1, TAO2, TAO3/JIK
<b>SPECIES</b>	Rat
<b>DOMAIN ORGANIZATION</b>	N-terminal kinase domain
<b>PHOSPHORYLATION SITES</b>	Ser <sup>181</sup>
<b>TISSUE DISTRIBUTION</b>	Brain
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	MEK3, MEK6
<b>UPSTREAM ACTIVATORS</b>	Sorbitol ( <b>S3755</b> ), Carbachol ( <b>C4382</b> )
<b>DOWNSTREAM ACTIVATION</b>	MEK3, MEK6
<b>ACTIVATORS</b>	Not known
<b>INHIBITORS</b>	Not known
<b>ISOZYME SELECTIVE ACTIVATORS</b>	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Activation of p38 pathway
<b>DISEASE RELEVANCE</b>	Prostate cancer

## FOOTNOTES