

Gene Section

Review

SRC (v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian))

Stephen Hiscox

Welsh School of Pharmacy, Redwood Building, Cardiff University, Cardiff, UK (SH)

Published in Atlas Database: April 2009

Online updated version: <http://AtlasGeneticsOncology.org/Genes/SRCID448ch20q11.html>

DOI: 10.4267/2042/44715

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Identity

Other names: ASV (Avian Sarcoma Virus); SRC1; c-SRC; p60-Src; pp60c-Src

HGNC (Hugo): SRC

Location: 20q11.23

Note

The Src kinase proto-oncogene has a high degree of similarity to the v-src gene of Rous sarcoma virus, although the C-terminal domain of v-Src is truncated and lacks the regulatory Tyr527 and therefore is not subjected to downregulation by Csk. Src kinase is implicated in the regulation of embryonic development, cell differentiation and proliferation. Src has been suggested to play a key role in cancer, where it may facilitate tumour spread through promotion of tumour cell invasion.

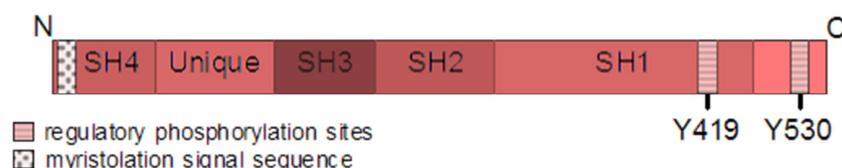
DNA/RNA

Note

The gene consists of 14 exons. Two isoforms have been described differing in their 5' UTRs. Variant 1 represents the longer transcript although both isoforms 1 and 2 encode the same protein.

Description

Size: 61.33 Kb, 14 exons. mRNA: 4145 bases.



Linear representation of the protein structure of human Src family members, showing the six distinct domains. N and C denote N- and C-termini respectively. Location of major regulatory phosphorylation sites and the myristoylation signal sequence are shown.

Protein

Note

Src can be phosphorylated on Tyr-530 by CSK (c-Src kinase). The phosphorylated form is termed pp60c-src. Phosphorylation of this tyrosine allows facilitates interaction between the C-terminal tail and the SH2 domain, maintaining Src in an inactive formation.

Protein Translation:

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MGSNKSKPKDASQRRRSLEPAENVHGAGGGAFP  
ASQTSPKASADGHRGPSAAFAPAAAEPKLFGGF  
NSSDVTSPQRAGPLAGGVTTFVALYDYESRTET  
DLSFKKGERLQIVNNTGDDWLAHSLSTGQTGY  
IPSNYVAPSDSIQAEWYFGKITRREGQGCFCGEV  
WMGTWNGTTRVAIKTLKPGTMSPEAFLQEAQV  
MKKLRHEKLVQLYAVVSEPIYIVTEYMSKGSLL  
DFLKGGETGKYLRPLQVDMAAQIASGMAYVER  
MNYVHRDLRAANILVGENLVCKVADFLGLARLIE  
DNEYTARQGAKFPIKWTAPAAALYGRFTIKSDV  
WSFGILLTELTKGRVPYPGMVNREVLQDQVERG  
YRMPCCPECPESLHDLMCQCWRKEPEERPTFEYL  
QAFLEDYFTSTEPQYQPGENL
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Note: This variant (isoform 1) represents the longer Src transcript although both isoforms 1 and 2 encode the same protein as the difference is in the 5' UTR.

Description

Size: 536 amino acids; 59.835 KDa.

Src is 59.6 KDa in size and has a domain structure comprised of six distinct functional regions (see figure above). These include an N-terminal SH4 domain that contains a lipid-modification sequence allowing targeting of Src to cellular membranes, and an adjacent, poorly-conserved region thus being unique to each Src family member. SH3 and SH2 domains adjacent to the N-terminus facilitate protein-protein interactions between Src and its interacting proteins whilst the SH1 domain allows ATP and substrate binding and has tyrosine kinase activity; autophosphorylation of Y419 within this domain is required for the maximum kinase activity of Src. The negative regulatory tail of Src contains a tyrosine at 530, the phosphorylation of which promotes a conformational change to produce an inactive Src molecule. Sequences within the C-terminus of Src have been recently identified to facilitate protein-protein interactions have been shown to regulate Src function in addition to its kinase activity.

Expression

Ubiquitously expressed but with particularly high levels in brain tissue, osteoclasts and platelets.

Localisation

Predominantly cytoplasmic and/or plasma membrane, the latter due to myristylation of the N-terminus. Activated Src has also been reported in the cell nucleus in some tumour tissues.

Function

Src can interact with a diverse array of cellular factors allowing it to regulate a variety of normal and oncogenic processes that ultimately result in cell proliferation, differentiation, survival, adhesion, motility, invasion and angiogenesis (Thomas and Brugge, 1997; Summy and Gallick, 2003). Such interacting partners include receptor tyrosine kinases (e.g. the EGF receptor family (Biscardi et al., 1998)), integrins (Gallagher and Schiemann, 2006; Huvener et al., 2007), cell-cell adhesion molecules (Giehl and Menke, 2008), in addition to STATs (Silva, 2004), FAK (Brunton and Frame, 2008), the adaptor protein p130Cas (Chang et al., 2008) and GPCRs (McGarrigle and Huang, 2007). Importantly, Src can also interact with the oestrogen receptor (Weatherman, 2008), where it has been shown to be pivotal in both non-genomic ER activation of signalling pathways and gene transcription events. The ability of Src to function as both an effector and regulator of receptor-induced signalling allows it to mediate cross-talk between normally distinct signalling pathways and thus regulate a wide variety of both normal and oncogenic processes, including proliferation, differentiation, survival, adhesion, motility, invasion and angiogenesis.

Homology

c-Src is the prototypic member of a family of nine non-receptor tyrosine kinases which share the same domain structure (Src, Fyn, Yes, Lyn, Lck, Hck, Blk, Fgr and Frk) (Erpel and Courtneidge, 1995) and are expressed in vertebrates. All Src family members have the same basic structure of an N-terminal, unique domain containing a myristylation site and frequently a palmitoylation site; regulatory SH3 and SH2 domains; a catalytic domain that has its active site wedged between the two lobes of the molecule, and a C-terminal regulatory tail that contains the hallmark regulatory tyrosine residue (Tyr527 in Src). The activity of Src family kinases is suppressed upon phosphorylation of Tyr527, allowing binding of the C-terminal domain to the SH2 domain. The SH2 and SH3 domains bind phosphotyrosine and proline-rich peptides, respectively; through these interactions, they participate in intra- and intermolecular regulation of kinase activity, as well as localization and substrate recognition. Differences in the SH2 linker sequences within Src family kinases correlate with the division of the Src kinase family into two separate subfamilies: Group A: Src, Fyn, Yes, Fgr and Group B: Lyn, Hck, Lck and Blk. Frk forms a separate but linked subfamily but with homologues also found in invertebrates. Src family members, with the exception of Src, Fyn and Yes, exhibit tissue-restricted distribution, being found primarily in cells of a haematopoietic nature. Below is a table constructed from Src homology analysis performed by CluSTr:

Src family member	% identity*	% similarity**
Fyn	75	10
Yes	73	9
Fgr	66	11
Lck	60	17
Lyn	60	17
Hck	57	17
Blk	62	13

*Percent identity between Src and protein; defined as: (Same AAs/Length of Protein 1) X100%

**Percent similarity between Src and protein; defined as: (Sim. AAs/Length of Protein 1) X100%

Mutations

Somatic

The SRC family of kinases is rarely mutated in primary human tumours, although apparently scarce, a truncating and activating mutation in Src (at aa 531) has been described for a small subset of advanced-stage colorectal cancers (Irby et al., 1999).

Implicated in

Cancer

Note

Elevated Src expression and/or activity has been reported in many different cancer types, where it may associate with poor clinical prognosis (Irby and Yeatman, 2000). Increased Src kinase activity in cancer is likely to arise from the deregulation of Src expression and/or activation mechanisms rather than the presence of activating mutations, since genetic mutations of this kind are rarely reported for Src (see above). Whereas constitutively activated forms of Src are transforming, wild-type Src has a relatively low transformation potential suggesting that Src may act to facilitate intracellular signalling through regulation, either directly or indirectly, of other signalling proteins.

Colorectal cancer

Disease

Increased Src activity has been widely described in colorectal tumour tissue compared with normal epithelia and within colon polyps, particularly those displaying a malignant phenotype (DeSeau et al., 1987; Cartwright et al., 1994). In colorectal cancer tissue studies, elevated Src kinase activity is associated with a poor clinical outcome (Aligayer et al., 2002). In vitro studies suggest that in colon cancer, Src may contribute more to disease spread than to increased proliferation (Jones et al., 2002).

Breast cancer

Disease

Src kinase activity is increased in breast cancer tissue compared to normal tissues (Verbeek et al., 1996). In vivo animal models suggest that Src activity is elevated in breast tumours over-expressing HER2 and interaction between Src and erbB family members may promote the development of a more aggressive disease clinically (Biscardi et al., 2000; Tan et al., 2005). Physical interactions between Src and growth factor receptors are reported in breast cancer tissues and cells, particularly with receptor tyrosine kinases of the EGFR family allowing Src to regulate signalling pathways that may contribute to aggressive breast cancer cell behaviour. Src is also intimately involved with Her2 pathway signalling in breast cancer, the result of which is the promotion of an invasive phenotype (Vadlamudi et al., 2003; Tan et al., 2005).

Oestrogenic signalling plays a critical role in promoting breast cancer cell growth where ligand-induced activation of oestrogen receptors (ERs) results in gene transcription mediated by the ER, in complex with various co-activators/co-repressor molecules. In such cases, Src is able to potentiate ER-mediated, AF-1 dependent gene transcription through indirect phosphorylation of nuclear ER via ERK1/ERK2 (Feng et al., 2001) and Akt (Campbell et al., 2001; Shah et al.,

2005) and through regulation of FAK-p130CAS-JNK signalling pathway activity and the subsequent activation of co-activator molecules including CBP (PAG1) and GRIP1 (NCOA2). Furthermore, Src appears to mediate non-genomic ER signalling through ERK and Akt pathways (Castoria et al., 2001; Wessler et al., 2006) to regulate cellular proliferation and survival (Castoria et al., 1999; Migliaccio et al., 2000). That Src is involved in both EGFR/Her2 and ER signalling has led to Src being implicated in growth factor-ER cross talk mechanisms in breast cancer and the development of endocrine resistance (Arpino et al., 2008; Massarweh and Schiff, 2006; Hiscox et al., 2006; Hiscox et al., 2009).

Hematopoietic cancers

Disease

The majority of Src family kinases are highly expressed in cells of a hematopoietic origin where they are suggested to regulate growth and proliferation. Src itself is, along with related family kinase members, are implicated in imatinib-resistant, BCR-ABL-expressing CML (Li, 2008).

Other tumour types

Disease

Src protein and activity have been identified as being increased in a number of other tumour types including gastric, pancreatic, lung and ovarian tumours compared to normal tissue suggesting a possible role for Src in these tumours.

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This article should be referenced as such:

Hiscox S. SRC (*v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)*). *Atlas Genet Cytogenet Oncol Haematol.* 2010; 14(3):301-304.
