

Src (gene)

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V-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)Protein_Data_BankPDB rendering based on 1a07.Available structuresProtein Data BankPDB 1A07, 1A08, 1A09, 1A1A, 1A1B, 1A1C, 1A1E, 1FMK, 1HCS, 1HCT, 1KSW, 1O41, 1O42, 1O43, 1O44, 1O45, 1O46, 1O47, 1O48, 1O49, 1O4A, 1O4B, 1O4C, 1O4D, 1O4E, 1O4F, 1O4G, 1O4H, 1O4I, 1O4J, 1O4K, 1O4L, 1O4M, 1O4N, 1O4O, 1O4P, 1O4Q, 1O4R, 1SHD, 1Y57, 1YI6, 1YOJ, 1YOL, 1YOM, 2BDF, 2BDJ, 2H8H, 2SRCIdentifiersHuman Genome OrganisationSymbols SRC; ASV; SRC1; c-SRC; p60-SrcExternal IDsMendelian Inheritance in ManOMIM: 190090 Mouse Genome InformaticsMGI: 98397 HomoloGene: 21120 GeneCards: SRC GeneEnzyme Commission numberEC number 2.7.10.2Gene OntologyMolecular function• nucleotide binding• protein kinase activity• protein kinase activity• protein tyrosine kinase activity• protein tyrosine kinase activity• non-membrane spanning protein tyrosine kinase activity• SH3/SH2 adaptor activity• protein kinase C binding• receptor binding• insulin receptor binding• integrin binding• protein binding• ATP binding• protein C-terminus binding• kinase activity• heme binding• SH2 domain binding• ion channel binding• cell adhesion molecule bindingCellular component• mitochondrion• mitochondrial inner membrane• cytosol• cytosol• plasma membrane• plasma membrane• caveola• postsynaptic density• synaptosomeBiological process• response to acid• protein phosphorylation• protein phosphorylation• response to stress• signal transduction• signal complex assembly• epidermal growth factor receptor signaling pathway• intracellular protein kinase cascade• Ras protein signal transduction• axon guidance• blood coagulation• cell proliferation• fibroblast growth factor receptor signaling pathway• response to mechanical stimulus• response to virus• positive regulation of gene expression• positive regulation of intracellular protein kinase cascade• positive regulation of glucose metabolic process• positive regulation of smooth muscle cell migration• cellular membrane organization• phosphorylation• cell-cell adhesion• peptidyl-tyrosine phosphorylation• platelet activation• forebrain development• T cell costimulation• response to nutrient levels• cellular response to insulin stimulus• regulation of estrogen receptor signaling pathway• positive regulation of integrin activation• cell junction assembly• response to drug• response to hydrogen peroxide• positive regulation of apoptosis• regulation of vascular permeability• interspecies interaction between organisms• transcytosis• regulation of bone resorption• bone resorption• positive regulation of cell adhesion• positive regulation of insulin receptor signaling pathway• platelet-derived growth factor receptor signaling pathway• nerve growth factor receptor signaling pathway• oogenesis• positive regulation of cytokine secretion• leukocyte migration• positive regulation of protein transport• response to mineralocorticoid stimulus• response to electrical stimulus• uterus development• branching involved in mammary gland duct morphogenesis• positive regulation of ERK1 and ERK2 cascade• response to interleukin-1• cellular response to lipopolysaccharide• cellular response to fatty acid• cellular response to protein stimulus• cellular response to hypoxia• positive regulation of canonical Wnt receptor signaling pathwaySources: Amigo / QuickGORNA expression pattern More reference expression dataOrthologsSpeciesHumanMouseEntrez 6714 20779Ensembl ENSG00000197122 ENSMUSG00000027646UniProt P12931 Q2M4I4RefSeq (mRNA) NM_005417.3 NM_001025395RefSeq (protein) NP_005408.1 NP_001020566Location (UCSC) Chr 20:35.97 – 36.03 Mb Chr 2:157.24 – 157.3 MbPubMed searchProto-oncogene tyrosine-protein kinase Src is an enzyme that in humans is encoded by the SRC gene.Anderson SK, Gibbs CP, Tanaka A, Kung HJ, Fujita DJ (May 1985). "Human cellular src gene: nucleotide sequence and derived amino acid sequence of the region coding for the carboxy-terminal two-thirds

of pp60c-src". *Mol. Cell. Biol.* 5 (5): 1122–9. PMC 366830. PMID 2582238. Src (pronounced "sarc" as it is short for sarcoma) is a proto-oncogene encoding a tyrosine kinase originally discovered by J. Michael Bishop and Harold E. Varmus, for which they won the 1989 Nobel Prize in Physiology or Medicine. "The Nobel Prize in Physiology or Medicine 1989: J. Michael Bishop, Harold E. Varmus". Nobelprize.org. 1989-10-09. . "for their discovery of 'the cellular origin of retroviral oncogenes'" It belongs to a family of non-receptor tyrosine kinases called Src family kinases. The discovery of Src family proteins has been instrumental to the modern understanding of cancer as a disease where normally healthy cellular signalling has gone awry. This gene is similar to the v-src gene of Rous sarcoma virus. This proto-oncogene may play a role in the regulation of embryonic development and cell growth. The protein encoded by this gene is a tyrosine-protein kinase whose activity can be inhibited by phosphorylation by c-SRC kinase. Mutations in this gene could be involved in the malignant progression of colon cancer. Two transcript variants encoding the same protein have been found for this gene. "Entrez Gene: SRC v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)". .v-src Francis Peyton Rous first proposed that viruses can cause cancer. He proved it in 1911 and was later awarded the Nobel prize in 1966. Chickens grow a tumor called a fibrosarcoma. Rous ground up these sarcomas, centrifuged them to remove the solid material, and injected the remaining liquid into chicks. The chicks developed sarcomas. The causative agent in the liquid was a virus, now called Rous sarcoma virus (RSV). Later work by others showed that RSV was a type of retrovirus. Non-cancer-forming retroviruses contain three genes, called gag, pol, and env. Some tumor-inducing retroviruses (such as RSV), however, also contain a gene called v-src (viral-sarcoma). It was found that the v-src gene in RSV is required for the formation of cancer and that the other genes have no role in oncogenesis. Stehelin D, Fujita DJ, Padgett T, Varmus HE, Bishop JM. (1977). "Detection and enumeration of transformation-defective strains of avian sarcoma virus with molecular hybridization". *Virology* 76 (2): 675–84. doi:10.1016/0042-6822(77)90250-1. PMID 190771. A function for Src tyrosine kinases in normal cell growth was first demonstrated with the binding of family member p56lck to the cytoplasmic tail of the CD4 and CD8 co-receptors on T-cells. Rudd CE, Trevillyan JM, Dasgupta JD, Wong LL, Schlossman SF (July 1988). "The CD4 receptor is complexed in detergent lysates to a protein-tyrosine kinase (pp58) from human T lymphocytes". *Proc. Natl. Acad. Sci. U.S.A.* 85 (14): 5190–4. doi:10.1073/pnas.85.14.5190. PMC 281714. PMID 2455897. . Src tyrosine kinases also transmit Cell adhesion integrin-dependent signals central to Cell (biology) cell movement and Cell growth proliferation. Hallmarks of v-src induced transformation are rounding of the cell and the formation of actin rich podosomes on the basal surface of the cell. These structures are correlated with increased invasiveness, a process thought to be essential for metastasis. v-src lacks the C-terminal end C-terminal inhibitory phosphorylation site (tyrosine-527), and is therefore constitutively active as opposed to normal src (c-src) which is only activated under certain circumstances where it is required (e.g. growth factor signaling). v-src is therefore an instructive example of an oncogene whereas c-src is a proto-oncogene. The first sequence of v-src was published in 1980 Czernilofsky AP, Levinson AD, Varmus HE, Bishop JM, Tischler E, Goodman HM (September 1980). "Nucleotide sequence of an avian sarcoma virus oncogene (src) and proposed amino acid sequence for gene product". *Nature* 287 (5779): 198–203. doi:10.1038/287198a0. PMID 6253794. and the characterization of sites for tyrosine phosphorylation in the transforming protein of Rous sarcoma virus and its normal cellular homologue was published in 1981. Smart JE, Oppermann H, Czernilofsky AP, Purchio AF, Erikson RL, Bishop JM (October 1981). "Characterization of sites for tyrosine phosphorylation in the transforming protein of Rous sarcoma virus (pp60v-src) and its normal cellular homologue (pp60c-src)". *Proc. Natl. Acad. Sci. U.S.A.* 78 (10): 6013–7. doi:10.1073/pnas.78.10.6013. PMC 348967. PMID 6273838. c-src In 1979, J. Michael Bishop and Harold E. Varmus discovered that normal chickens contain a gene that is structurally closely related to v-src. The normal cellular gene was called c-src (cellular-src). Oppermann H, Levinson AD, Varmus HE, Levintow L, Bishop JM (1979). "Uninfected vertebrate cells contain a protein that is closely related to the product of the avian sarcoma virus transforming gene (src)". *Proc Natl Acad Sci U S A.* 76 (4): 1804–8. doi:10.1073/pnas.76.4.1804. PMC 383480. PMID 221907. This discovery changed the current thinking about cancer from a model wherein cancer is caused by a foreign substance (a viral gene) to one where a gene that is normally present in the cell can cause cancer. It is believed that at one point an ancestral virus mistakenly incorporated the

c-src gene of its cellular host. Eventually this normal gene mutation mutated into an abnormally functioning oncogene within the Rous sarcoma virus. Once the oncogene is transfected back into a chicken, it can lead to cancer.

src: The Cancer transforming (sarcoma inducing) gene of Rous sarcoma virus. The protein product is pp60^{vsrc}, a cytoplasmic protein with tyrosine-specific protein kinase activity (Enzyme Commission number EC 2.7.10.2), that associates with the cytoplasmic face of the plasma membrane. The protein consists of three domains, an N-terminal SH3 domain, a central SH2 domain and a tyrosine kinase domain. The SH2 and SH3 domains cooperate in the auto-inhibition of the kinase domain. c-Src is phosphorylated on an inhibitory tyrosine near the c-terminus of the protein. This produces a binding site for the SH2 domain which, when bound, facilitates binding of the SH3 domain to a low affinity polyproline site within the linker between the SH2 domain and the kinase domain. Binding of the SH3 domain results in misalignment of residues within the kinase domain's active site inactivating the enzyme. This allows for multiple mechanism for c-Src activation: dephosphorylation of the C-terminal tyrosine by a protein tyrosine phosphatase, binding of the SH2 domain by a competitive phospho-tyrosine residue, as seen in the case of c-Src binding to focal adhesion kinase, or competitive binding of a polyproline binding site to the SH3 domain, as seen in the case of the HIV NEF protein.

Model organisms

Src knockout mouse phenotype

Characteristic

Phenotype

Homozygote viability Normal

Fertility Normal

General Observations

Abnormal

Body weight Normal

Open_Field_(animal_test) Anxiety Normal

Neurological assessment Normal

Grip strength Normal

Hot_plate_test Hot plate Normal

Dysmorphology Normal

Indirect calorimetry Normal

Glucose tolerance test Normal

Auditory brainstem response Normal

Dual-energy_X-ray_absorptiometryDEXA Normal

Radiography Normal

Body temperature Normal

Eye morphology Normal

Clinical chemistry Normal

Haematology Normal

Peripheral blood lymphocytes Normal

Micronucleus test Normal

Heart weight Normal

Brain histopathology Normal

Salmonella infection Normal

"Salmonella infection data for Src". Wellcome Trust Sanger Institute. .

Citrobacter infection Normal

"Citrobacter infection data for Src". Wellcome Trust Sanger Institute. .

All tests and analysis from Gerdin AK (2010). "The Sanger Mouse Genetics Programme: high throughput characterisation of knockout mice". *Acta Ophthalmologica* 88: 925-7. doi:10.1111/j.1755-3768.2010.4142.x: Wiley. .

Mouse Resources Portal, Wellcome Trust Sanger Institute.

Model organisms have been used in the study of SRC function. A conditional knockout mouse line, called Src^{tm2a}(EUCOMM)Wtsi "International Knockout Mouse Consortium". . "Mouse Genome Informatics". . was generated as part of the International Knockout Mouse Consortium program — a high-throughput mutagenesis project to generate and distribute animal models of disease to interested scientists.

Skarnes, W. C.; Rosen, B.; West, A. P.; Koutsourakis, M.; Bushell, W.; Iyer, V.; Mujica, A. O.; Thomas, M. et al (2011). "A conditional knockout resource for the genome-wide study of mouse gene function". *Nature* 474 (7351): 337–342. doi:10.1038/nature10163. PMID 21677750.

Dolgin E (June 2011). "Mouse library set to be knockout". *Nature* 474: 262-263. doi:10.1038/474262a. .

Collins FS, Rossant J, Wurst W (January 2007). A mouse for all reasons. *Cell* 128(1): 9-13. doi:10.1016/j.cell.2006.12.018 PMID 17218247.

Male and female animals underwent a standardized phenotypic screen to determine the effects of deletion.

van der Weyden L, White JK, Adams DJ, Logan DW (2011). "The mouse genetics toolkit: revealing function and mechanism". *Genome Biol* 12 (6): 224. doi:10.1186/gb-2011-12-6-224. PMID 21722353. .

Twenty four tests were carried out on mutant mice and one significant abnormality was observed. Homozygote mutant animals were found to viable, but lacking teeth. Due to the severity of the homozygous phenotype, the remaining tests were carried out on heterozygous mutant adult mice; no additional significant abnormalities were observed in these animals.

Interactions

Src (gene) has been shown to Protein-protein interaction

interact with Androgen receptor

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