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Src

Regulation and function in the exocrine pancreas

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Gene Symbol: Src

Alternate Names: Src, c-Src, pp60-Src

1. General Information

The discovery of Src family of non-receptor tyrosine kinases dates back a century ago (1911) when Peyton Rous noted tumors transmissible in chicken via cell free extracts (37). This eventually culminated in the discovery of the Rous Sarcoma virus gene product which was subsequently shown to cause tyrosine phosphorylation of proteins (15). V-Src i.e. the viral protein was thus the first described proto-oncogene, and c-Src is its normal cellular homologue in animals (41). Src family members play key roles in cell morphology, endocytosis, motility, proliferation and survival. There are 11 members in the family (Blk, Brk, Fgr, Frk, Fyn, Hck, Lck, Lyn, c-Src, Srm, and Yes) of which some are expressed in pancreatic acinar cells.

Structure and Regulation

The Src family kinases are about 60 KD in size and human c-Src has 536 amino acids, with the 3 additional amino acids inserted at the N terminus compared to chicken Src (533 amino acids). Src has a myristolyation sequence at the N terminus followed by 4 SH (Src homology) domains. The first one of which, i.e. the SH4 unique domain is 80 amino acids followed by a SH3 (81-145), a SH2 (151-248), a protein kinase (SH1) domain (273-523) and a C terminus sequence with intervening linker regions (Figure 1). The two established sites of regulation of are tyrosine 527 (Y527) located 6 amino acids from the C-terminus and Tyrosine 416 (Y416).

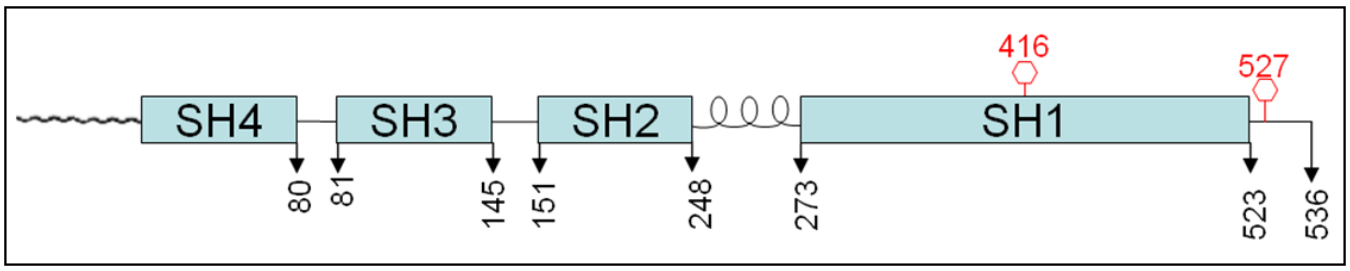

Figure 1: Diagram showing Domain structure of Src. The numbers indicate amino acids numbered starting from the N terminus. The wavy line preceding the SH4 domain is the 14 carbon myristolyation sequence. The proline rich domain (PRD) is indicated by the left handed helix connecting the SH2 and SH1 domains. The tyrosine phopshorylation sites are indicated by a red line with the hexagon.

The SH1 kinase domain of Src is bilobed and has an ATP binding region at the amino portion and a protein substrate binding area on the carboxy portion. The carboxy portion contains the activation loop with tyrosine 416, the phopshorylation of which stabilizes the active conformation. The functions of each domain are shown in table 1. For more detail the reader is referred to more extensive, excellent reviews on the structure and regulation of Src (4, 35, 36, 47).

Domain	Function
SH4	Unique to each member. Has 14 carbon myristoyl group at N terminus which may help in membrane localization.
SH3	Binds PRD (249-272) intramolecularly keeping Src inactive. Potential substrates with PRDs may bind SH3, relocate Src and activate it.
SH2	Binds, stabilizes phosphorylated Y527 keeping Src inactive. A protein with phosphotyrosines may bind SH2, relocate Src and activate it.
SH1	The kinase domain. Y416 phosphorylation occurs with activation.
C-terminal regulatory segment	Y527 phosphorylation (e.g. by Csk, Chk) results in binding of SH2 thus stabilizing inactive Src. Dephosphorylation by Shp1, Shp2, PTP1B etc. may increase Src activity by dissociating from it from the SH2 domain.

Table 1: Table showing functions of the various domains of Src.

2. Pancreatic Information

Localization and Binding

Src normally shows a membraneous location in acinar cells, with apical enrichment under normal conditions and is associated with cortactin (39) (Figure 2). Activation of Src by supraphysiologic caerulein changes the staining pattern of Src and Yes to a cytosolic one along with its dissociation from cortactin (39). This activation also increases the binding of Src to RhoA (26) and the P85 subunit of PI3 kinases (25).

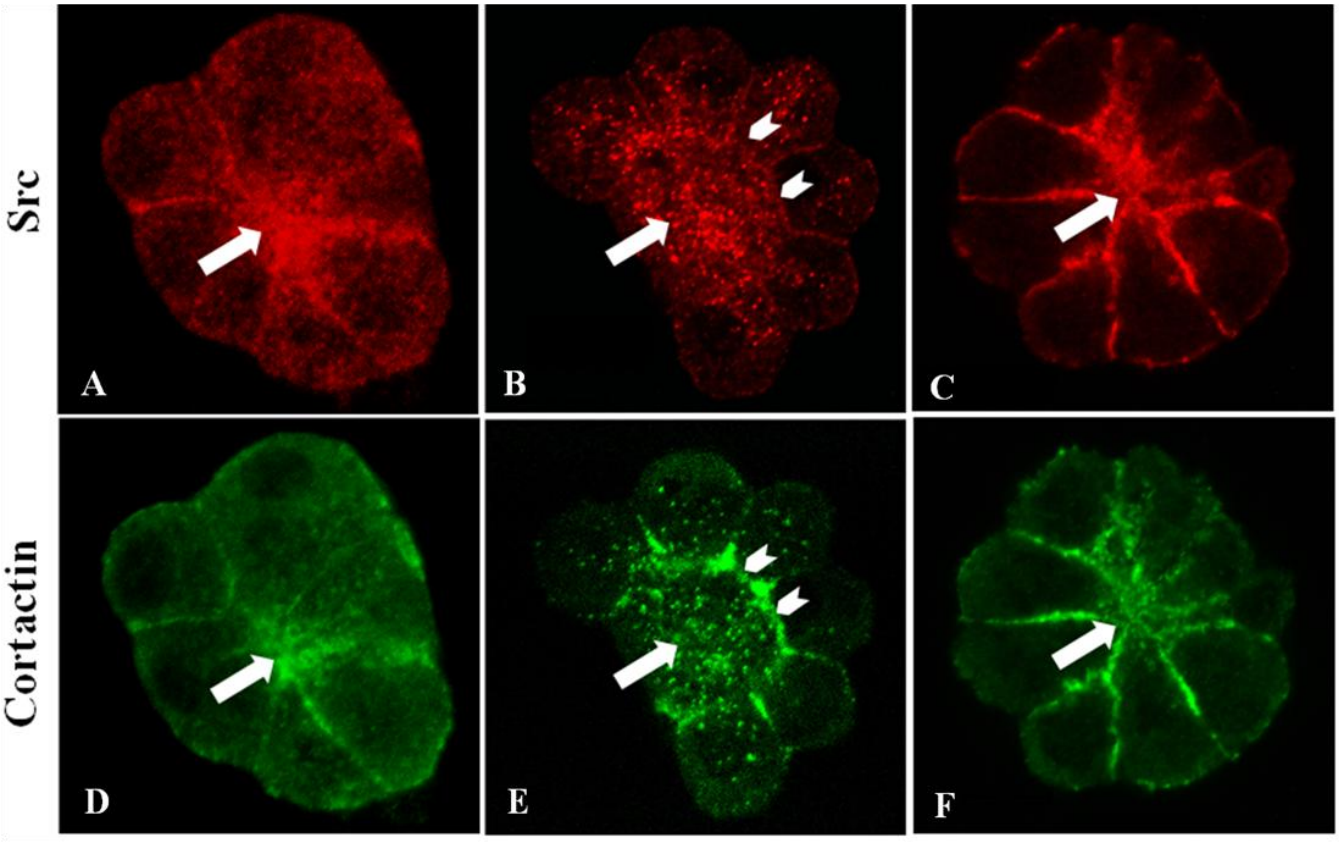

Figure 2: Src and Cortactin normally co-localize apically in acinar cells and localize differentially with supraphysiologic stimulation: Immunostaining of Src (A-C) and Cortactin (D-F) in acinar cells under control conditions (A, D) shows both to localize apically (Arrows). Treatment 10nM caerulein for 30 minutes (**B, E**). results in a diffuse cytosolic appearance of Src (**B**) while cortactin localizes on the basal surface (**arrowheads, E**). The Src inhibitor PP2 prevents these caerulein induced changes, retaining both on the apical surface (**C, F**). Modified from Mol Biol Cell. 2008 May;19(5):2339-47.

Activation

Numerous studies (2, 13, 19, 22, 30, 31, 33, 34) have shown that diverse stimuli activate Src in pancreatic acinar cells. Yes and Lyn are both know to be activated by supraphysiologic doses of CCK (22, 30, 39). However Lyn is also shown to be activated by physiologic doses of CCK, EGF, and phorbol ester (30). Activation occurs rapidly in response to caerulein, with maximal phosphorylation of Y416 detected within 1-2 minutes (30, 39). Some studies suggest that Src activation may be calcium dependent (52).

Src family members have been hypothesized to play several roles in acinar cells including the regulation of store mediated calcium entry (34) by c-Src, changes in actin localization by Yes (19, 22), secretion by Src and Yes (22, 25), activation of PKC-delta by Lyn (45), upregulation of chemokine production in response to substance P via the neurokinin-1 receptor (33), endocytosis (13, 31), and acinar cell blebbing via Yes mediated phosphorylation of cortactin (39). Pharmacologic inhibition of Src results in a reduction in the severity of caerulein induced pancreatitis in both rats (39) and mice (33). Acinar phenomena in which the role of Src has been studied in detail are discussed below.

Calcium Homeostasis

Redondo et al showed that depletion of the intracellular calcium stores with thapsigargin induces Src activation (34). This is dependent on

the integrity of the actin cytoskeleton, since it was prevented by cytochalasin D, which prevents actin polymerization. Conversely the Src inhibitor PP1 dose dependently reduced store mediated calcium entry (34). Tsunoda et al using a kinase assay showed that substrate phosphorylation was reduced in extracts from acini incubated in the presence of the extracellular calcium chelator EGTA (51). The exact mechanism by which Src is regulated by calcium or vice versa remains to be explored.

Actin Localization and Blebbing

Pancreatic acinar cells normally have filamentous actin (F-actin) enriched in the subapical area (27, 28, 39, 40). This reorganizes, with an increase on the basolateral surface, when acinar cells are stimulated with supraphysiologic doses of caerulein (1, 39, 40, 48, 49). Acinar blebbing induced by supraphysiologic caerulein is dependent on the actin cytoskeleton (48). The Src family member Yes has been thought to play a role in basolateral reorganization of F-actin (22, 39). Lutz et al showed that the Src inhibitor PP1 partially prevented actin changes (22). We have shown Src dependent tyrosine phosphorylation of the protein cortactin which regulates the branching of actin (39). Preventing cortactin phosphorylation, by pharmacologic inhibition of Src using PP2 or SU6656, or transfection of acini with a mutant cortactin which cannot be tyrosine phosphorylated by Src reduced baso-lateral reorganization of actin induced by supraphysiologic caerulein. Additionally, the pathological blebbing that is induced by supraphysiologic caerulein was also prevented by the mutant cortactin and pharmacologic inhibition of Src.

Pancreatic Cancer

Studies in pancreatic cancer have shown Src to be involved in tumorigenesis, cell proliferation, invasion, and motility. C-Src and oncogenic RAS have been shown to co-operatively initiate and accelerate pancreatic cancer (38). Aberrant acinar cell expression of the CCK2 receptor under the elastase promoter was associated with Src activation, formation of preneoplastic lesions and pancreatic tumor development (11). Src dependent activation of phosphatidyl inositol-3 kinase and p38 MAPK have been shown to be involved in expression of receptors for vascular endothelial growth factors (VEGF) and the angiogenic potential of pancreatic cancer (43).
Endocytosis, vesicular transport through the Golgi in pancreatic cancer cells is known to be regulated via phosphorylation of the large GTPase dynamin-2 (55) and its associated actin-binding protein, cortactin (5). Phosphorylation of Dynamin-2 at tyrosines 231, 579 by Src has also been shown to be involved in the metastatic migration and invasion of pancreatic tumor cells lines (10).

Pharmacologic inhibition of Src has been shown to inhibit progression and metastasis in orthotopic (50) and transgenic (23) models of pancreatic cancer. The Src inhibitor Dasatinib (BMS-354825) resulted in decreased phosphorylation of extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinase (MAPK), focal adhesion kinase (FAK), paxillin, AKT, signal transducers and activators of transcription 3 (STAT3), as well as decreased cyclin D1 expression. This prevented anchorage-independent growth, proliferation, migration, invasion, cell cycle progression while stimulating apoptosis (24).

3. Tools for studying Src in acinar cells

a. Antibodies

Src family: (SC-18, Santa Cruz biotechnology) Polyclonal antibody, use 1:500 for WB.
Phospho-Src (Tyr416): (catalog # 2101, Cell Signal), Rabbit polyclonal antibody raised against a phosphopeptide; use 1:1000 for WB.

b. Inhibitors

Pharmacologic inhibition of Src has is indispensable in determining Src's function in various acinar biologic processes. This remains the main approach for phenomena such as trypsinogen activation that significantly diminish in cultured acinar cells or are not replicated by exocrine cell lines such as AR42J cells.

The Src inhibitors used include the pyrazolo-pyrimidine compound PP1 (16) (4-Amino-5-(4-methylphenyl)-7-(t-butyl)pyrazolo[3,4-d]-pyrimidine), and the related PP2 (4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-d]-pyrimidine) which act as competitive inhibitors of ATP binding. However PP1 has been shown to inhibit PDGF-β receptor (53) directly along with inhibiting Ret (6), c-Kit and Bcr-Abl (46). SU6656 (2-oxo-3-(4,5,6,7-tetrahydro-1H-indol-2-ylmethylene)-2,3-dihydro-1H-indole-5-sulfonic acid dimethylamide), was synthesized as a more specific inhibitor of Src (3). The IC_{50} of all these agents for various Src family members (except PP1 which has an IC_{50} of 6nM for Lyn) ranges from 20-280nM (29). Dasatinib (BMS-354825; N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]amino)]-1,3-thiazole-5-carboxamide) inhibits both the Src family kinases and Bcr-Abl with an IC_{50} of < 1nM (8). Despite the other targets PP1, PP2, and Dasatinib when used at appropriate concentrations for short term studies remain invaluable, since c-Abl is not normally expressed as a protein in acinar cells (unpublished data). However caution may need to be exercised in studies pertaining to PDGF since PDGFR-β is expressed in acinar cells and the levels of both PDGFR-β and its ligand are increased in chronic disease (9). Further relevant details of inhibitors are available in excellent reviews (7, 29, 44).

c. Activation

The commonly used methods for studying Src activation are:

1. Immuno-precipitation and western blotting for active Src (PY416).
2. Src kinase activity assays.

Src Kinase assays have been used previously in acinar cells (22, 51). These are quantitative, and can be done on both cell lysates and immuno precipitated Src family members. Various substrates (e.g. PKS2-biotin substrate, $p34^{cdc2}$ [6-20]) have been used by different groups (22, 51). We (39) and others (30) have used the widely published method of determining the amount of active Src. This is described elsewhere.

d. Mouse Lines

While pharmacologic inhibition of Src has proven to be beneficial in rat caerulein pancreatitis (39), the role of individual Src family members in pancreatitis remains to be determined. While there are redundancies in their functions, triple knock outs of Src, Yes and Fyn are embryonically lethal (18). Studies of mice genetically deficient in individual Src family members suggest their role in several of the mechanisms relevant to pancreatitis. For example c-Src-/- mice have reduced vascular permeability which minimizes the damage resulting from ischemia reperfusion injury (32) such as in stroke or myocardial infarction (54). Lyn -/- mice have defects in immunoglobulin-mediated signaling, suggesting that it has a role in establishing B cell tolerance (17). While genetic knock outs of Fyn display defects in T cell signaling (42), dual knock outs for Hck, Fgr display defects in innate immunity as evidenced by (20, 21) defective neutrophil adhesion and migration and macrophages from triple knock outs of Hck, Fgr and Lyn display defects in Fcgamma receptor-mediated phagocytosis (12).

4. Summary

While some Src family members such as Yes have been implicated in specific functions of acinar cells including actin dynamics, and the role of Src in pancreatic carcinogenesis, growth and

invasion is being explored; the roles other Src family members may play in acinar cell physiology or diseases such as pancreatic cancer, acute pancreatitis remains to be determined.

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