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The Role of Src in Solid Tumors

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Abstract

The proto-oncogene c-Src (Src) is a nonreceptor tyrosine kinase whose expression and activity is correlated with advanced malignancy and poor prognosis in a variety of human cancers. Nine additional enzymes with homology to Src have been identified and collectively are referred to as the Src family kinases (SFKs). Together, SFKs represent the largest family of nonreceptor tyrosine kinases and interact directly with receptor tyrosine kinases, G-protein-coupled receptors, steroid receptors, signal transducers and activators of transcription and molecules involved in cell adhesion and migration. These interactions lead to a diverse array of biological functions including proliferation, cell growth, differentiation, cell shape, motility, migration, angiogenesis, and survival. Studies investigating mutational activation of Src in human cancers suggest this may be a rare event and wild-type Src is weakly oncogenic. Thus, the role of Src in the development and progression of human cancer has remained unclear. Recently, it has been suggested that increased SFK protein levels and, more importantly, SFK tyrosine kinase activity is linked to cancer progression and metastatic disease by facilitating the action of other signaling proteins. This accumulating body of evidence indicates that SFKs may represent a promising therapeutic target for the treatment of solid tumors. This review discusses the role of SFKs in solid tumors and the recent therapeutic advances aimed at targeting this family of tyrosine kinases in cancer.

Keywords

c-Src; solid tumors; Src family kinases; molecular inhibitors

Src and the Src Family Kinases

Src was first identified as the cellular form of v-Src, the transforming gene product of the avian Rous sarcoma virus [1, 2]. Src has been strongly implicated in the development, maintenance, progression, and metastatic spread of several human cancers such as prostate, lung, breast, and colorectal. Since the discovery of the Src proto-oncogene in 1976, nine additional variants closely related to Src have been identified in the human genome and collectively termed the Src family kinases (SFKs) [3, 4]. In general, SFKs are subdivided into three distinct groups primarily based upon their general pattern of expression (Table 1). The first group (Src, Fyn, and Yes) is ubiquitously expressed. The second group (Blk, Fgr, Hck, Lck, Yrk and Lyn) is found primarily in hematopoietic cells, and the third group (Frk-related kinases) is expressed predominantly in epithelial-derived tissues [5–8]. Although these proteins are classified based upon their expression in various tissues, it is also widely recognized that alternatively spliced isoforms, as well as the level of expression and activity, play a role in their cellular function.

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Src Family Kinases Structure and Activation

Structurally, SFKs are highly related to one another and contain conserved structural elements between family members (Fig. 1). These elements include the N-terminal Src Homology 4 domain (SH4), the Src Homology 3 domain (SH3), Src Homology 2 domain (SH2), a linker sequence, the tyrosine kinase domain, and the C-terminal tail [9]. The N-terminal domain, SH4, serves as a site for myristoylation and thus targets SFKs to the cytoplasmic membrane. The SH3 domain binds amino acid sequences rich in proline residues [10]. This domain is critical for Src activity, intracellular localization, and the recruitment and binding of Src substrates. The SH2 domain binds to short motifs containing phosphotyrosines. Together, the SH2 and SH3 domains cooperate in regulating SFKs catalytic activity (Fig. 2).

In the inactive conformation, Src contains a phosphorylated tyrosine at position 530 in humans, which interacts with its own SH2 domain. This positions the SH3 domain to interact with the proline-rich linker domain and keeps Src in a tightly bound inactive state. Upon dephosphorylation of tyrosine 530, the intramolecular interactions are destabilized ultimately resulting in the autophosphorylation of tyrosine 419 [11–13]. This series of events then allows the opening of the molecule and frees the SH2 and SH3 domains to interact with receptor tyrosine kinases, G-protein-coupled receptors, and focal adhesion kinase (FAK) (Fig. 3).

Once activated, Src is involved in the regulation of normal and oncogenic processes including proliferation, differentiation, survival motility, and angiogenesis (Fig. 4). However, it is well established that overexpression of wild-type Src is weakly oncogenic on its own [14]. Furthermore, a number of investigators have shown that mutations leading to the constitutive activation of Src in human cancers are rare [15–19]. Taken together, the poor transformation potential of Src, coupled with the lack of mutational activation in human cancers has clouded our understanding of Src in the development, maintenance, and progression of cancer. Recent evidence has suggested that overexpression of wild-type Src may promote the activity of other signaling molecules in contrast to being a lone dominant transforming agent [20]. Indeed, Src has been shown to interact with several proteins including receptor tyrosine kinases (colony-stimulating factor 1 receptor [CSF-1R], platelet derived growth factor receptor [PDGFR], vascular endothelial growth factor [VEGFR], epidermal growth factor receptor [EGFR], human epidermal growth factor receptor 2 [HER2], HER3) [2]. Other interaction partners include signal transducers and activators of transcription (STATs), heterotrimeric G proteins, the mitogen-activated protein kinase ERK2, cyclins D and E, and FAK [21, 27]. In antigen-presenting cells, the SFK Fyn has been shown to be recruited and activated by SLAM-family proteins via interactions with its SH3 domain [22].

With the re-emergence of SFKs in cancer, intense efforts have been made to identify and characterize agents that possess inhibitory activity to SFKs. These small molecules function by interfering with the kinase domain or blocking the SH2 and SH3 domains from entering the conformation necessary for activation. Most notably of these agents are dasatinib (BMS-354825), bosutinib (SKI-606), AZD-0530, INNO-406 (NS-187), and XL-228. These agents exhibit a variety of mechanisms of action and have often shown marked efficacy in preclinical and clinical settings (Table 2). This review addresses the latest studies that strengthen the role of Src and SFKs in solid tumor types and their potential as therapeutic targets.

Src and Src Family Kinase Molecular Targeting Agents in Development

Dasatinib (Sprycel ®, Bristol Myer Squibb), also known as BMS-354825, is the only FDA approved SFK inhibitor for use in chronic myeloid leukemia (CML) or Philadelphia-chromosome positive acute lymphocytic leukemia (ALL). Several phase II and III clinical trials regarding its use in CML, and ALL have reported, and others are ongoing. Phase I and II trials regarding dasatinib's use in non-hodgkin's lymphoma, metastatic breast and prostate cancer, refractory leukemia in adolescents, and other metastatic cancers are also ongoing. Dasatinib has the potential for becoming a beneficial treatment for solid tumors.

Bosutinib (SKI-6606; Wyeth) is a dual kinase inhibitor of both SFK's and Abl. There are currently clinical trials studying bosutinib's effect in imatinib resistant CML (phase I, II, and III) as well as two closed clinical trials using bosutinib in breast cancer (phase II) and advanced malignant solid tumors (phase I).

AZD-0530 (AstraZeneca) is a dual tyrosine kinase inhibitor of both SFK's and Abl. There are several phase II studies ongoing using AZD-0530 all of which include metastatic cancer or cancer refractory to standard chemotherapies (i.e., breast cancer, non-small cell lung cancer, sarcoma, head and neck squamous cell carcinoma, prostate cancer, thymoma, thymic carcinoma, pancreatic cancer, ovarian cancer, and adenocarcinoma of the stomach or gastroesophageal junction).

XL-999 (Exelixis) is a receptor tyrosine kinase with several targets including VEGFR, PDGFR, FGFR, Src, and FLT3 (FMS-like tyrosine kinase 3). A phase II trial was initiated using XL-999 in four solid tumors: renal cell carcinoma, colon cancer, ovarian cancer, and non-small cell lung cancer. The FDA suspended the trial in 2006 due to adverse cardiovascular events. However, recently a phase I trial in non-small cell lung cancer was reinitiated in 2007.

INNO-406 (NS-187; CytRx), also known as NS-187, is also a dual kinase inhibitor of Abl and Lyn (Src family kinase) and is structurally similar to nilotinib. It was intended for CML imatinib-resistant patients with Lyn overexpression.

KX01 (KX2-391; Kinex) is a recent addition to the Src inhibitor class. This drug targets the peptide-binding domain of SFKs and has been shown to suppresses oncogenic proliferation in vitro and in vivo it is currently being tested in phase I clinical trials [23,24].

XL-228 (Exelixis) is a molecule that blocks several tyrosine kinases receptors such as insulin-like growth factor 1 receptor (IGF-1R), SFK's, and Bcr-Abl. The Bcr-Abl blockade includes the mutant form of Abl (T315I), which has been correlated with imatinib-resistant CML and Philadelphia chromosome-positive acute lymphocytic leukemia (ALL). Currently XL-228 is in phase I trials with ALL, CML, and advanced malignancies.

Src and SFKs in Prostate Cancer

SFKs and Src perform important functions in the oncogenesis of prostate cancer. Src, and the SFKs Lyn and Fgr are expressed in high levels in malignant tissues and primary cell cultures derived from the prostate [25, 26]. Treating primary prostate cells with the Lyn-inhibitor KRX-123 resulted in a reduction of cell proliferation, migration, and invasive potential *in vitro* [26, 27]. Furthermore, the activity of SFKs has been implicated in androgen-induced proliferation of malignant cells derived from the prostate. These data extend to *in vivo* models, such that tumor growth in mice resulted in reduced disease progression and metastasis when treated with a Src-inhibitor [28–30].

The development of therapies to address unregulated Src signaling in the prostate is already in progress and preclinical evidence for effective treatment with dasatinib is enticing. Dasatinib has been shown to suppress proliferation of PC-3 human prostate cancer cells [31], as well as inhibit the poor adhesion, increased migration, and potential invasiveness of the DU145 human prostate cancer cell line [25]. Signals originating from Src and Lyn were also mitigated, as measured by the diminished activity of FAK and secreted proteases in DU145 cells. In addition, dasatinib treatment of mice injected with PC-3 cells resulted in diminished tumor development [29].

Recently, a phase II study was initiated to test the efficacy of dasatinib in hormone-refractory prostate cancer patients. Patients with progressive metastatic prostate cancer, a rising prostate-specific antigen (PSA), testosterone <50 ng/dL, and no prior chemotherapy were recruited for this study. Preliminary results indicated 10 of 15 RECIST-evaluable patients exhibited disease control (67%) [32]. A ≥35% decrease in UNTx excretion (a marker of bone resorption) was noted among 57% of evaluable patients. These early clinical results are the first and only efficacy data for SFK inhibition in a solid tumor setting and appear promising for the potential application of SFK inhibitors in prostate cancer treatment.

Phase II trials of AZD-0530 are also currently in progress. One study is evaluating AZD-0530 in patients with hormone-refractory prostate cancer, and another is comparing the efficacy and safety of AZD-0530 agent to zoledronic acid in patients with prostate cancer who also have metastatic bone disease.

Src and SFKs in Colorectal Cancer

The study of colon cancer has yielded some of the most compelling evidence of the central role of SFKs in cancer progression. Bolen et al. showed that Src expression levels are increased 5–8 fold in premalignant polyps versus normal mucosa with more elevated concentrations identified in adenocarcinoma tissue [33–35]. These expression levels have been found to correlate not only to tumor stage, size, and metastatic potential but also to progression-free survival and overall survival of the patient [36, 37]. Further investigation also identified Src kinase activity in premalignant colitis lesions, and determined that the greatest amount of dysplasia in these injuries often resulted in the most potential for progression to advanced stages [38].

In addition to increased Src activity and expression levels, the activity of Yes has been reported in premalignant tissues in the colon. This activity correlates with disease progression [39, 40]. Preclinical investigation supports a role for Yes, in that both Src and Yes have been shown to become activated after estradiol treatment of cells derived from colon carcinoma [41]. The expression of Lck was identified in colon carcinoma cell lines, which is particularly intriguing due to the typically hematopoietic origin of cells expressing this SFK [42]. However, little additional data on the role of Lck in colon cancer has been obtained, and further investigation in this area should prove informative.

Current treatment modalities for human colorectal cancer often favorably combine targeted inhibitors of EGFR with cytotoxic agents. However, the development of resistance to these agents is a perpetual challenge and a role for Src in this process has been identified [43–46]. Kopetz and colleagues were able to restore sensitivity to cetuximab-resistant cell lines when treated with dasatinib [47]. There appeared to be a synergistic effect between these two agents, which resulted in the enhanced modulation of Src with this combination. In addition, preclinical studies suggest that Src blockade can restore sensitivity to cetuximab in cetuximab resistant cells [48]. A phase I study evaluating dasatinib in combination with florinic acid, fluorouracil, oxaliplatin (FOLFOX) and cetuximab treatment [49] is in progress.

A phase II trial studying how well AZD-0530 performs in patients with previously treated metastatic colon cancer or rectal cancer is also underway. There is also a phase II study of XL-999 administered intravenously to patients with metastatic colorectal cancer that was recently completed, but the results for this trial have not yet been reported. These trials represent an exciting new undertaking for incorporating Src inhibition in combination with other targeted agents or chemotherapies for a promising approach to novel colorectal cancer treatment.

Src and SFKs in Breast Cancer

Breast cancer exhibits altered signal transduction pathways involving Src [50]. Evidence of increased SFK activity and protein expression levels has been found in human breast cancer tissue relative to normal tissue [51–53]. Two transgenic mouse models first highlighted the prominent role of Src in breast cancer. Mammary tumors were induced by the oncogenic expression of polyoma virus middle T antigen. The transforming ability of the middle T antigen, in part, is due to its ability to associate with and to activate several SFKs (Src, Yes, and Fyn) [54]. Another model by Muthuswamy et al. discovered a 6- to 8-fold higher Src signaling in transgenic HER2/neu mice, a molecule related to the EGFR receptor tyrosine kinase and found overexpressed in 20—25% of human breast cancer [55]. The increased amounts of Src signaling were confined to malignant tissue only and were not accounted for by elevated expression levels alone.

Collectively, these data present a clinical rationale for targeted inhibition of SFKs in a breast cancer setting. Recent data showed dasatinib in conjunction with the nucleoside analog gemcitabine in patients with breast tumors was tolerable [56]. Response and survival data were not reported in this phase I study, but the safety profile among these patients is encouraging, and further investigation is ongoing.

The interaction between estrogen signaling and SRK inhibition is also being investigated. The overexpression of the estrogen receptor (ER) in the nucleus of breast cancer cells has an established role in cell-cycle regulation while conferring tumor growth responsiveness to steroid hormones [57]. In a study of breast cancer cells expressing either wild-type or a hypersensitive mutant ER, wild-type cells responded to estrogen stimulation by increasing Src kinase activity. In hypersensitive mutants, the basal Src activity was much higher than wild-type, and the artificial addition of estrogen had no further effect [58]. However, steroid hormones receptors like ER do not require binding of ligand to invoke signaling cascades and ER-mediated changes in gene expression and the activation of SFKs have occurred independent of estrogen exposure [59].

A randomized, open-label, phase II study of bosutinib in combination with exemestane as second-line treatment for locally advanced or metastatic breast cancer is currently underway. This trial will be key in the evaluation of the combined inhibition of ER signaling and Src inhibition in the clinical setting. Lastly, a phase II trial of AZD-0530 in patients with metastatic or locally advanced breast cancer that cannot be removed by surgery is also in progress.

There is also evidence that Src inhibitors may have a role in treating HER2-positive breast cancer. Preclinical evidence has shown that Src binds to HER2 and is activated in HER2-positive breast cancer cells, permitting PI3K signaling via phosphatase and tensin homolog (PTEN) inactivation [60]. Furthermore, anti-HER2 antibody trastuzumab causes dissociation of Src from HER2, inactivating Src, and consequently inhibiting HER2-mediated PI3K pathway signaling. This evidence supports the rational combination of Src inhibitors and trastuzumab in HER2-positive breast cancer.

Breast cancer that is hormone receptor- and HER2-negative ("triple-negative" breast cancer) has few treatment options and has a poor prognosis. Preliminary data from a phase II study of single-agent dasatinib in women with locally advanced or metastatic triple-negative breast cancer suggest a tumor response rate of 5% and a clinical benefit rate of 9% [61]. This modest, but encouraging, activity supports further studies to address optimal dasatinib dosing and combination with chemotherapy in this disease.

Src and SFKs in Lung Cancer

The activities of Src, SFKs, and their downstream effectors have strong implications in the etiology of non-small cell lung cancer (NSCLC). The inhibition of Src in EGFR-dependent NSCLC cell lines was shown to result in growth signaling shutdown and the induction of apoptosis [62]. The expression of Src substrates STAT3 and FAK are often found in NSCLC tissues, and immortalized cell lines derived from these tissues [63]. STAT3 activity is modulated by the presence of a variety of growth factors and stimulation by each of these requires functional Src [64].

The relationship between receptor tyrosine kinase signaling and effector molecules downstream of Src was highlighted by Sordella et al. Mutations in EGFR that activate the STAT pathway were found to confer resistance to chemotherapy and a heightened sensitivity to inhibitors of EGFR like gefitinib and erlotinib [65]. Other receptor tyrosine kinases like VEGFR may also function similarly as evidenced by the activation of STAT3 that is observed in human lung adenocarcinoma during periods of hypoxia, resulting in increased blood flow to nascent tumors deprived of oxygen [66, 67]. It appears likely that Src-mediated signaling in the progression of malignancy extends beyond growth-factor induced phenomena to include additional homeostatic regulatory mechanisms in the cell. This potential further emphasizes the application of targeted inhibition of SFKs in the effective treatment of nascent tumors of the lung.

Given the clear rationale for targeting SFKs and EGFR many of the latest therapies that are effective in the treatment of NSCLC involve inhibition of these molecules [68–70] (Fig. 4). For instance, two therapies effective for patients with NSCLC are gefitinib and erlotinib, which are small molecules that inhibit EGFR and consequently reduce activation of Src and its substrates, including STAT3 [68, 71]. These therapies underscore the role of tyrosine kinase signaling and implicate Src as a prominent molecular target in the treatment of lung cancer [72].

Evaluating the use of these agents in combination is in progress. A phase I trial has commenced that evaluates the potential for simultaneous EGFR and SFK inhibition. Chiappori and colleagues demonstrated that combination therapy with erlotinib and dasatinib in patients with advanced NSCLC is tolerable [73]. The safety profile for both of these agents was consistent with the known adverse events (rash and pleural effusion). The efficacy of this therapy is currently being ascertained and preliminary results will be of interest.

Currently, a phase II trial of AZD-0530 in patients with recurrent, stage IIIB or stage IV NSCLC that was previously treated with chemotherapy combination regimens is recruiting patients. There is a placebo-controlled study of AZD-0530 in patients with recurrent osteosarcoma localized to the lung underway as well. A dose finding and tolerability study XL-999 in patients with NSCLC is also in progress.

Src and SFKs in Head and Neck Cancer

Less is known of the effect of Src inhibition in other aerodigestive settings such as head and neck squamous cell carcinoma (HNSCC). HNSCC has shown evidence of SFK overexpression (Src, Yes, Fyn, and Lyn), and signaling through STAT3 and STAT5 proteins [74–76]. Inhibition of SFKs led to reduced STAT activation, and decreased growth in cell lines derived from HNSCC malignancies [76]. Investigation by Grandis and colleagues revealed STAT3 activation was able to increase cell survival via abrogation of apoptosis in tumors of the head and neck *in vivo* [77]. Additionally, STAT3 activity has been shown to eliminate growth factor dependence and contribute to HNSCC tumor growth [78].

Src- and SFK-targeted compounds are currently being evaluated for efficacy and safety in patients with HNSCC. Investigation of dasatinib in preclinical models of HNSCC yielded an increase in apoptosis and decrease in cell division as well as inhibition of the migratory and invasive potential of cancer cells [79]. AZD-0530 is also being evaluated, and preliminary results show decreased Src levels accompanied by reduced cell proliferation and invasion in treated cell lines derived from HNSCC [80]. AZD-0530 is also being tested in combination with gefitinib in preclinical breast cancer models, but preliminary results have not yet been reported.

Src and SFKs in Pancreatic Cancer

Src and SFKs play a prominent role in pancreatic cancer [81]. High levels of Src have been detected in tumor tissues and cell cultures derived from pancreatic malignancies [82]. The SFK Lyn has also been found expressed above basal levels in the PANC-1 immortalized cell line [83]. In addition, signal modulation by Src has been identified for a number of proteins that are found overexpressed in pancreatic tumors. These include growth factor receptors, carcinoembryonic antigen-related adhesion molecule 6 (CEACAM6), and cholecystokinin-2 (CCKR2) [84–86]. Furthermore, an increase in the expression of the insulin-like growth factor-1 (IGF-1) results from activation Akt signaling downstream of Src (Fig. 4) [87]. This causes an increase in the cell's proliferative ability and provides an additional mechanism for SFKs to contribute to tumorigenesis in the pancreas.

The nucleoside analog gemcitabine has been used successfully to treat pancreatic cancer for over 10 years. However, resistance to this agent is also a significant therapeutic challenge. Abrogating Src signaling has been shown to restore sensitivity to gemcitabine in tumor and tissue transplants cell lines derived from the pancreas [45,46,88]. A similar result was obtained when FAK expression was silenced in PANC-1 cells treated with gemcitabine. Recent preclinical evidence suggests that inhibition of Src also reverts chemoresistance against 5-fluorouracil in human pancreatic carcinoma cells [89].

The targeted inhibition of EGFR has proved to be an effective therapy in treating pancreatic cancer. The tyrosine kinase inhibitor (TKI) erlotinib was approved for patients with pancreatic cancer and favorable outcomes were obtained when used in combination with gemcitabine [90]. Overall survival was extended with the combination regimen after one-year (24% versus 17%) and event-free survival increased to 6.4 months from 5.9. These data are modest by clinical assessment, but represent an important proof-of-concept for the role of targeted therapy in mitigating tumorigenesis of the pancreas. This was further supported by additional studies investigating the role of TKIs in pancreatic cancer that were conducted recently. A small study investigated a combination of cediranib with AZD-0530 in treating patients with pancreatic tumors. The available data are limited, but this combination appears to have a tolerable safety profile [91].

Src and SFKs in Cancers of the Nervous System

The role of SFK in the brain and neuronal tumors is not as extensively studied as solid tumors deriving from the breast, lung, colon, prostate, or pancreas. However, neuronal tissues do exhibit increased expression of Src and Fyn, and it is likely that these proteins play a role in the deregulated proliferation and uninhibited growth of tumors arising in the nervous system [92]. Indeed, one study correlated FAK expression to the development of astrocytomas in the brains of mice [93]. Furthermore, neuroblastoma cell lines have been shown to express Src at levels much higher than that observed in primary cultures from noncancerous tissues of the central nervous system (CNS) [94]. Neuroendocrine tumors have also exhibited elevated Src expression, which correlates with the differentiation state of the tumor [95]. Further preclinical modeling is necessary, but preliminary clinical evidence indicates that dasatinib can cross the bloodbrain barrier and consequently reduce the burden of CNS Ph+ ALL [96]. This suggests that oral dasatinib may be effective against a number of CNS malignancies.

One CNS malignancy dasatinib may have clinical activity against is glioblastoma multiforme. Preclinical evidence indicates that dasatinib inhibits cell viability and migration *in vitro* and tumor growth *in vivo*, and exerts these actions through inhibition of Src [97]. Safety results of a phase II study of dasatinib following treatment with temozolomide and radiotherapy for patients with recurrent glioblastoma multiforme were recently reported [98]. The toxicity observed was relatively mild despite a 100 mg twice-daily dose. There were no grade 4 or 5 adverse events reported. These data are encouraging, but further research is necessary to uncover the full role of SFK inhibition in cancers developing in the CNS.

Other Tumor Types

There is substantial evidence implicating the Src pathway in melanoma and other tumor types [99]. Preclinical studies have shown dasatinib to have anti-proliferative and anti-invasive effects against melanoma cell lines, and to induce apoptosis in sarcoma cells [100–102]. Also, in ovarian cancer models, Src inhibition has been shown to have antiangiogenic effects and to significantly reduce tumor burden [103]. Clinical studies of dasatinib in solid tumors, including these tumor types, are currently underway. Investigations of AZD-0530 in osteosarcoma, melanoma, and ovarian tumors are in progress. XL-999 is currently being evaluated in kidney and ovarian disease settings.

Conclusions and Future Directions

Accumulating evidence suggests an important role for SFKs in solid tumors from a variety of tissues. The array of receptors that trigger SFK activity and the subsequent activation of downstream effectors present a compelling therapeutic target for treatment modalities in cancer management. SFK directed TKIs have potential use as single-agent therapy in some disease states. However in other forms of cancer, like malignancies of the breast, there is only a limited amount of evidence obtained that implicates single-agent SFK inhibition as a potentially effective intervention. Src's involvement with numerous growth and cell metabolism functions suggests combinations with chemotherapeutics is worth additional evaluation. Preclinical and early phase trial data suggest compelling combination regimens with targeted therapies, such as a Src/SFK inhibitor and an EGFR inhibitor, would warrant further investigation.

The array of tyrosine kinase inhibitors with activity against Src and other SFKs is noteworthy (Table 2), and presents a considerable possibility for future investigation. These agents also feature different affinities for Src/SFK inhibition, as well as separate inhibitory

activity against other molecules, suggesting variations in binding potential as well as mechanism of action within the class. Dasatinib is FDA approved for the treatment of imatinib-resistant chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphocytic leukemia (Ph+ ALL). Bosutinib is currently in phase II/III clinical trials and will likely be available for future clinical usage in the near future. AZD-0530 and XL-99 are currently being investigated in phase II trials.

These drugs, coupled with existing molecular targeting agents or other molecules, cytotoxins, radiotherapy, and surgical interventions present a wide array of new therapeutic approaches to evaluate. Ongoing work continues to highlight the most effective of these that will control the aberrant intracellular signaling that is the hallmark of oncogenesis.

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The abbreviations used are

ALL	acute lymphocytic leukemia
CEACAM6	carcinoembryonic antigen-related adhesion molecule 6
CCKR2	cholecystokinin-2
CML	chronic myelogenous leukemia
CNS	central nervous system
CRC	colorectal cancer
CSF-1R	colony-stimulating factor 1 receptor
EGFR	epidermal growth factor receptor
ER	estrogen receptor
FAK	focal adhesion proteins
FDA	food and drug administration
FOLFOX	florinic acid, fluorouracil, oxaliplatin
HER	human epidermal growth factor receptor
HNSCC	head and neck squamous cell carcinoma
IGF-1	insulin-like growth factor 1
NSCLC	non-small cell lung cancer
PDGFR	platelet-derived growth factor receptor
PSA	prostate specific antigen
SH2	Src homology 2 domain
SH3	Src homology 3 domain
SH4	Src homology 4 domain
SFK	Src-family kinases
STAT	signal transducer and activator of transcription

TKI	tyrosine kinase inhibitor
VEGFR	vascular endothelial growth factor receptor

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Learning Objectives

- Src and SFKs are important signaling molecules involved in an array of cellular functions.
- Unregulated Src and SFK activity contributes to oncogenesis and development of solid tumors in a variety of tissues.
- Targeting Src and SFKs for inhibition can result in positive therapeutic outcomes and represents a novel approach in cancer therapy.

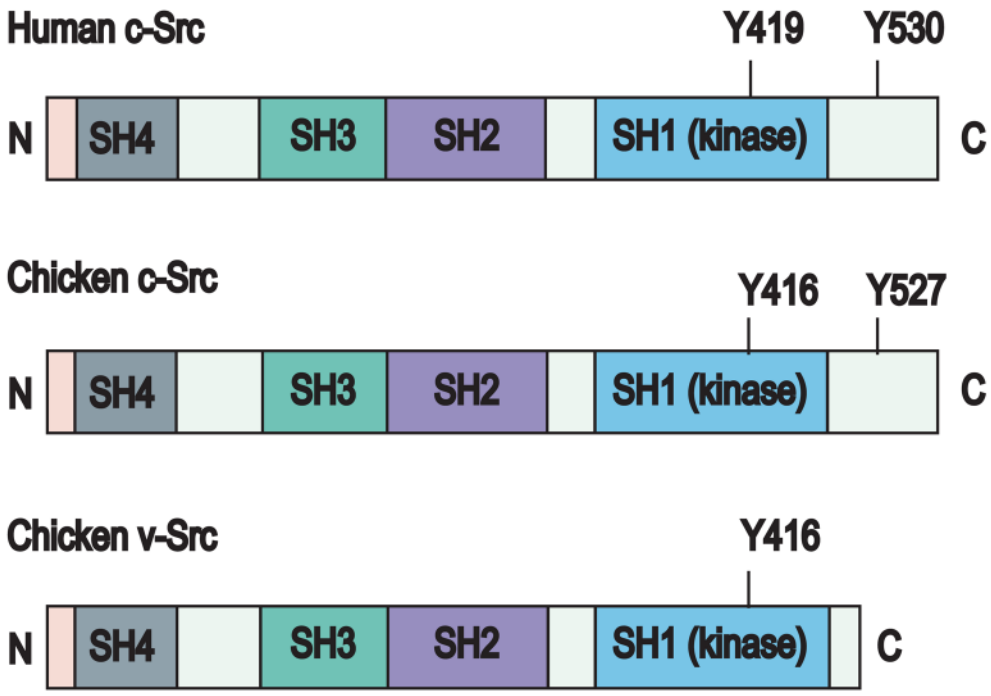

Figure 1.
Comparison of the molecular structures of human c-Src, chicken c-Src, and chicken v-Src. All three proteins contain four Src homology (SH) domains and a unique amino-terminal domain of unknown function. The SH1 domain contains the kinase domain and a conserved tyrosine residue involved in autophosphorylation (Tyr419 in human c-SRC; Tyr416 in chicken). Chicken v-Src lacks the carboxy-terminal negative-regulatory domain and contains 12 substituted carboxy-terminal amino acids, as well as numerous point mutations throughout the molecule, explaining the high level of activity of this protein.
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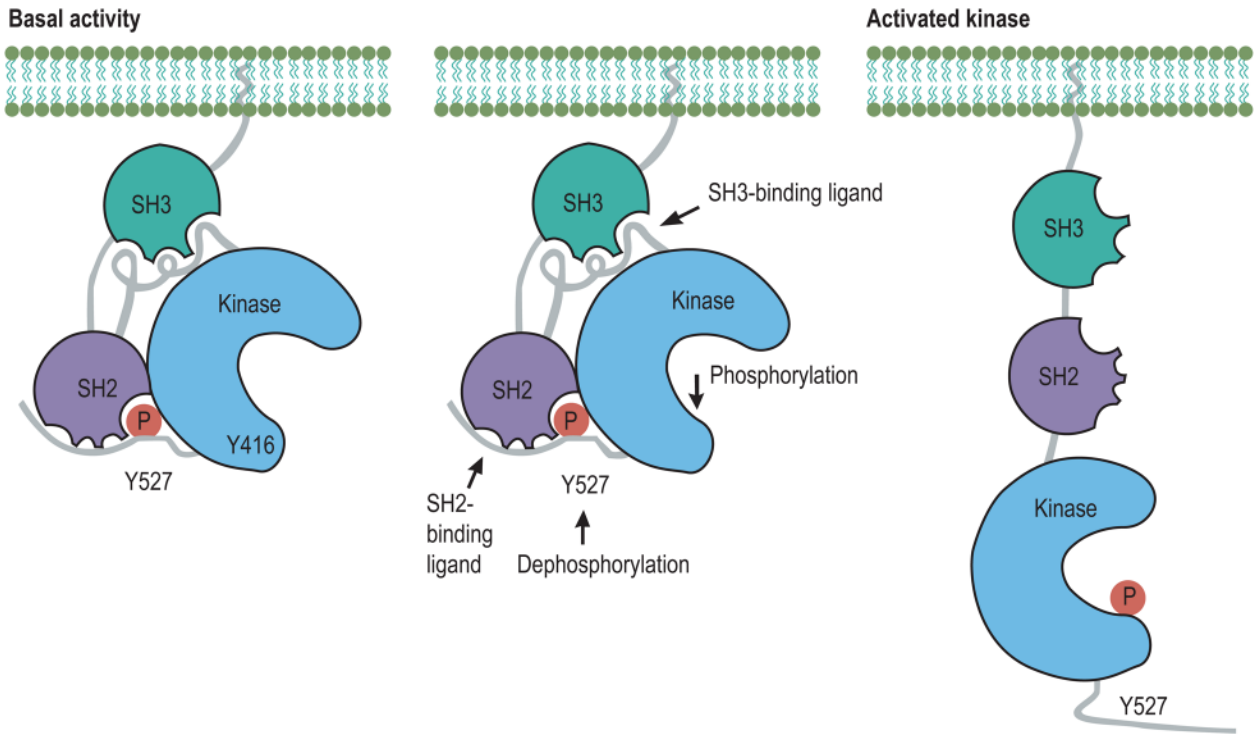

Figure 2.
Activation of c-Src. The left panel represents the inactive conformation of Src in which Tyr527 (chicken c-Src) interacts with the SH2 domain, positioning the SH3 domain to interact with the linker between the SH2 and catalytic domains. The middle panel illustrates different mechanisms involved in the activation of Src, and the right panel represents the open or active conformation.
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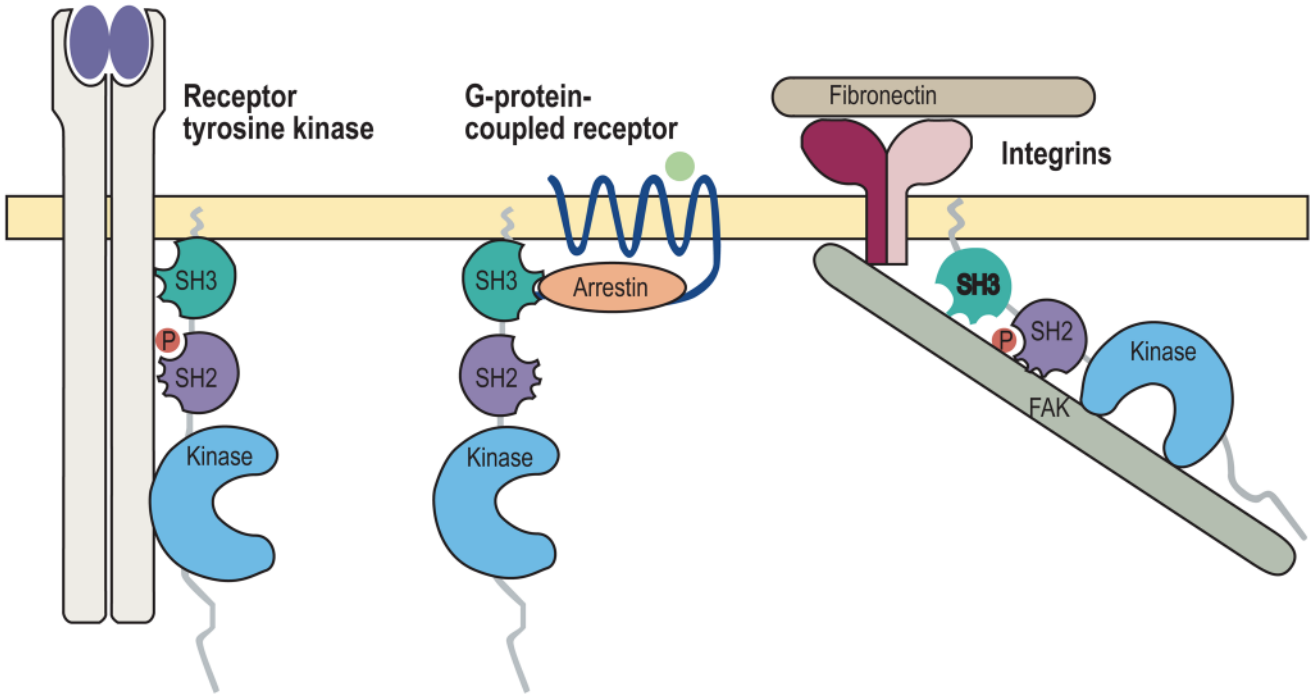

Figure 3.

Postulated regulation of c-Src by surface receptors. Src can be activated by several types of cell surface or cytoplasmic receptor. Shown here is, from left to right, a receptor tyrosine kinase such as the platelet-derived growth factor receptor; a G-protein-coupled receptor such as the β-adrenergic receptor; and an integrin bound to extracellular matrix. In each case, Src is activated by binding of a ligand to the SH2 and/or SH3 domains. In the case of a receptor tyrosine kinase, the SH2 ligand is a phosphotyrosine residue of the autophosphorylated receptor. In the case of the β-adrenergic receptor, the SH3 ligand is a proline motif of β-arrestin bound to the receptor. In the case of an integrin, the SH2 ligand is a phosphorylated tyrosine residue of autophosphorylated focal adhesion kinase (FAK).

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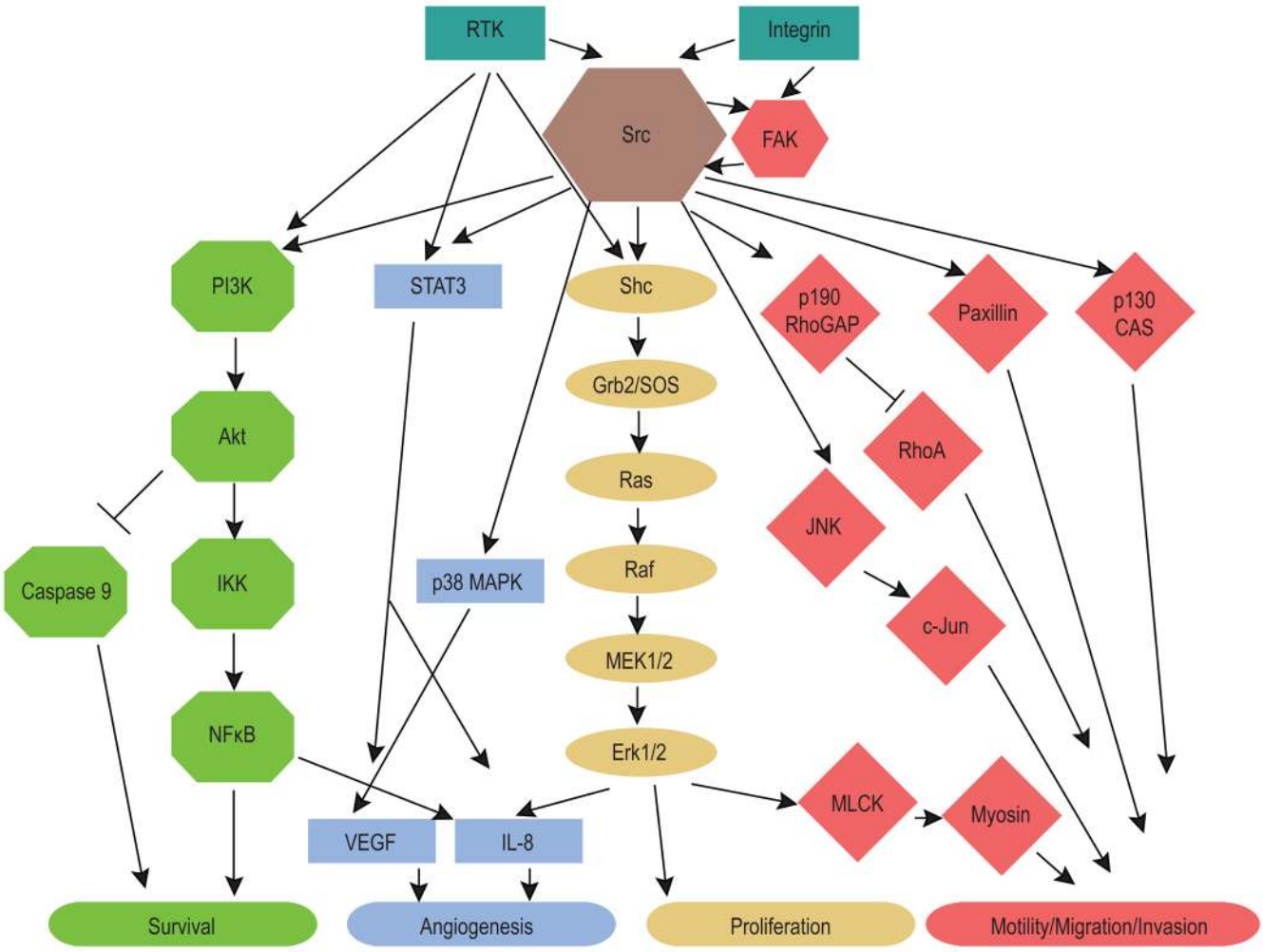

Figure 4.

Selected examples of Src signal transduction pathways. CAS = Crk-associated substrate; ERK = extracellular signal-regulated kinase; FAK = focal adhesion kinase; IKK = IkB kinase; IL-8 = interleukin 8; JNK = Jun N-terminal kinase; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase kinase MAPK/ERK kinase; MLCK = myosin light chain kinase; NFKB = nuclear factor kB; PI3K = phosphatidylinositol 3-kinase; RhoGAP Rho GTPase-activating protein; RTK = receptor tyrosine kinase; SOS = son of sevenless; STAT3 = signal transducer and activator of transcription 3; VEGF = vascular endothelial growth factor.

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Table 1

The Src family kinases

Gene	Expressing Tissues	Subfamily	Chromosomal Locus
Src	ubiquitous	SrcA	20q11
Fyn	ubiquitous	SrcA	6q21
Yes	ubiquitous	SrcA	18q2
Hck	myeloid, lymphoid	SrcB	20q11
Lck	lymphoid	SrcB	1p35
Lyn	myeloid, prostate, pancreatic	SrcB	8q13
Blk	myeloid	Other	8p22
Frk	pancreatic, kidney, breast	Other	6q21
Yrk	Neural, hematopoietic tissues	Other	1p36
Fgr	leukocytic	Other	1p36

Table 2

Src and Src Family Kinase Molecular Targeting Agents in development

Agent	Sponsor	Target	Target Site	Solid Tumor Setting[a]
Dasatinib	BMS	BCR-ABL, SFKs, ABL, Kit, PDGFRβ, Eph receptors	ATP-Binding	SCLC, NSCLC, Breast, CRC, HNSCC, Liver, melanoma, ovarian, pancreatic, sarcomas
Bosutinib (SKI-606)	Wyeth	ABL, SFKs	ATP-Binding	Breast
AZD-0530	AstraZeneca	SFKs, ABL	ATP-Binding	SCLC, NSCLC, Breast, CRC, HNSCC, osteosarcoma, melanoma, ovarian, pancreatic, prostate
XL-999	Exelixis	SFKs, VEGFR2, PDGFR, Kit, and FGFR1	ATP-Binding	NSCLC, CRC, kidney, ovarian[b]
INNO-406	CytRx	ABL, SFKs	ATP-Binding	No current relevant trials
KX01	Kinex	Src	Peptide-binding	Phase I
XL-228	Exelixis	BCR-ABL, ABL, SFKs, IGF-R1	ATP-Binding	Phase I

CML, chronic myeloid leukemia; CRC, colorectal cancer; FGFR, fibroblast-derived growth factor;. HNSCC, head and neck squamous cell carcinoma; IGF-1R, insulin-like growth factor receptor; NSCLC, non-small cell lung cancer; PDGFRβ, platelet-derived growth factor β; Ph+ ALL, Philadelphia-chromosome positive acute lymphoblastic leukemia; SCLC, small cell lung cancer; SFK, Src family kinases;

[a] Information from www.clinicaltrials.gov. Accessed May 14th 2009.

[b] Studies were terminated due to safety concerns.