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Targeting SRC in glioblastoma tumors and brain metastases: rationale and preclinical studies

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Abstract

Glioblastoma (GBM) is an extremely aggressive, infiltrative tumor with a poor prognosis. The regulatory approval of bevacizumab for recurrent GBM has confirmed that molecularly targeted agents have potential for GBM treatment. Preclinical data showing that SRC and SRC-family kinases (SFKs) mediate intracellular signaling pathways controlling key biologic/oncogenic processes provide a strong rationale for investigating SRC/SFK inhibitors, eg, dasatinib, in GBM and clinical studies are underway. The activity of these agents against solid tumors suggests that they may also be useful in treating brain metastases. This article reviews the potential for using SRC/SFK inhibitors to treat GBM and brain metastases. Word count =99/100

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1. Introduction

WHO grade III gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma) and grade IV gliomas (glioblastoma or GBM and gliosarcoma) are collectively referred to as malignant gliomas. GBM is the most common primary CNS tumor, accounting for 50% of the 17000 primary brain tumors diagnosed annually in the US [[1, 2]]. GBM occurs in all age groups with two discrete peaks of incidence in patients aged 0-8 years [[3]] and 45-70 years [[4]]. GBMs are infiltrative tumors, able to migrate to and invade areas of normal brain, and regardless of treatment, GBM almost always recurs, highlighting the need for novel therapies to treat this tumor.

Histologically, GBM is characterized by hypercellularity, atypical nuclei, increased proliferation, increased microvasculature and dilated vessels (angiogenesis), invasion of adjacent brain, and evidence of necrosis (particularly in large tumors that likely have hypoxic cores) [[1]]. Until recently, GBMs were thought to be derived from astrocytes based on their frequent expression of glial fibrillary acidic protein (GFAP), an intermediate filament and marker of astrocytes; however, GBMs have been shown to contain a proliferative tumorinitiating population of cells termed glioma stem cells [[5, 6]].

GBMs are extremely aggressive tumors and are associated with a dismal prognosis. Untreated patients typically die within 3 months and progression usually occurs within 6-9 months from initial diagnosis, even among those who receive the most current treatment. Approximately 25% of patients survive for 2 years and fewer than 10% survive for 5 years [[1]]. The current standard of care for newly diagnosed GBM is surgical resection, followed by concomitant radiotherapy and temozolomide (TMZ) chemotherapy for 6 weeks, then adjuvant TMZ for 6-12 months. The efficacy of this approach was demonstrated in a phase III trial ($n = 573$) conducted by the European Organisation for the Research and Treatment of Cancer and the National Cancer Institute of Canada [[7]]. Patients who received concurrent radiotherapy and TMZ followed by adjuvant TMZ had a higher median survival than those who received radiotherapy alone (14.6 and 12.1 months, respectively). The 2-year overall survival (OS) rate was more than double with combination therapy compared with radiotherapy alone (26.5% and 10.4%, respectively).

Recently, single-agent bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) with antiangiogenic activity, was approved by the FDA for treatment of recurrent GBM. Bevacizumab with or without irinotecan was well tolerated and increased the estimated historical 6-month progression-free survival (PFS) rate from 15% to 43% and 50%, respectively [[8, 9]]. To date, bevacizumab has not been shown to improve OS. Two ongoing randomized phase III studies in patients with newly diagnosed GBM are investigating the efficacy of first-line bevacizumab combined with TMZ and radiotherapy (NCT00884741; NCT00943826) (see ClinicalTrials.gov). Even if ongoing trials demonstrate prolonged OS with bevacizumab, novel therapies are still needed to inhibit GBM invasion, extend duration of treatment response, or provide additional options to prevent disease recurrence.

Although bevacizumab prolonged PFS in patients with recurrent GBM, resistance to antiangiogenic (or anti-VEGF) therapy is expected. Two main mechanisms of resistance to anti-VEGF therapy are thought to exist: (i) during prolonged VEGF sequestration, tumor vasculature continues to grow via VEGF-independent neoangiogenesis (e.g., via basic fibroblast growth factor release); and (ii) glioma cells co-opt the host vasculature to invade normal brain without promoting angiogenesis. Preclinical models suggest that anti-VEGF therapy can induce a previously noninvasive glioma tumor to invade normal brain [[10-12]].

In these examples, bevacizumab does not block tumor invasion but rather promotes it underscoring the need for combination therapies that block GBM invasion.

Although GBM is the most common primary CNS tumor, metastatic tumors to the CNS also have a poor prognosis and limited treatment options. Brain metastases are a frequent complication of many solid tumor types, particularly breast cancer, lung cancer, and melanoma [[13]]. Although brain metastases have diverse tumors of origin, standard treatment involves surgical resection of accessible tumors and/or whole-brain radiotherapy, which can be combined with stereotactic radiosurgery [[14]]. Because whole-brain irradiation can negatively affect normal brain function, including cognition, additional therapeutic options are needed.

Further work is needed to develop novel targeted agents for patients with CNS tumors. Specifically, there is a critical need to develop therapies that target invading GBM cells. In this review, evidence supporting the evaluation of agents targeting SRC kinase or SRC-family kinase (SFK) members in GBM is discussed. The potential for using SRC inhibitors in the treatment of brain metastases is also considered.

2. SRC and SFKs as anticancer targets

Targeted therapies block growth, invasion or progression of tumor cells by interfering with signaling molecules or pathways important for the malignant phenotype. Identification of proteins with GBM-specific upregulation/activation or defects in expression may reveal potential novel targets. Based on this hypothesis, phase I and II trials are underway to investigate targeted agents that inhibit a range of targets, including inhibitors of integrins (cilengitide), tenascin (131I-81C6), phosphatidylinositol-3-kinase (PI3K; XL765), tyrosine kinases (sorafenib), and matriolytic enzymes (prinomostat) [[15]].

Accumulating data demonstrate that SRC kinase and SFKs are promising targets for anticancer therapy. The viral homolog of the *SRC* gene, *v-SRC*, was discovered as an extension of studies to identify a transmissible noncellular agent that promoted formation of chicken sarcomas [[16]]. The Rous sarcoma virus, which encoded *v-SRC* was responsible for malignant transformation [[17]]. Subsequent research found a gene in normal avian DNA closely related to *v-SRC* that was named cellular *Src* (represented as *c-Src* in early publications), which was the first proto-oncogene to be identified [[18]]. Structurally, *v-SRC* protein lacks the negative regulatory C-terminal domain of SRC and has several point mutations, resulting in constitutive activation of *v-SRC* and the potential to induce malignant transformation [[19-21]].

SFKs are a group of homologous nonreceptor tyrosine kinases with highly conserved structures consisting of four SRC-homology domains (SH1-4), a tyrosine kinase domain, and a C-terminal negative regulatory domain [[22]]. SFKs mediate intracellular signaling from multiple cell surface proteins, including growth factor receptors, integrins, and the EPH family of kinases. SFKs also bind to key intracellular signaling proteins, notably focal adhesion kinase (FAK) and the related proline-rich protein tyrosine kinase (PYK2/PTK2B) [[23, 24]]. Through these interactions and others, SFKs perform essential roles in regulating normal cellular processes, including cytoskeletal organization and remodeling that accompanies cell adhesion, motility, and cell division.

3. Activation and regulation of SRC

Much of what has been learned regarding SFK activation and function was derived from studies of *c-SRC* protein. SRC is maintained in an inactive state by C-terminal SRC kinase (CSK)-mediated phosphorylation of a negative-regulatory tyrosine residue (Y530). When

phosphorylated, Y530 binds to the SH2 domain, folding SRC into an inactive configuration [[22]]. Negative regulation of SRC by CSK can have powerful antimetastatic and antiinvasive effects, as demonstrated by CSK overexpression in metastatic mouse colon carcinoma cell lines [[25]]. For SRC activation, the Y530 residue is dephosphorylated by protein tyrosine phosphatase- α [[26]], allowing the SRC structure to unfold into an active configuration that permits access of substrates to the kinase domain [[22]]. SRC can also be activated by direct binding of its SH2 and SH3 domains to intracellular proteins (e.g., FAK, the adaptor molecule p130^{CAS}, or the actin filament-associated protein AFAP-110), or to activated tyrosine kinase growth factor receptors (e.g., epidermal growth factor receptor [EGFR] family members EGFR1 and human epidermal growth factor receptor-2 [HER2], platelet-derived growth factor receptor [PDGFR], VEGF receptor [VEGFR], and fibroblast growth factor receptor). Interaction between SRC and these proteins disrupts intramolecular inhibitory interactions within SRC, resulting in its activation [[21, 27, 28]].

Cell adhesion promotes association of FAK with SFKs [[29]]. FAK was first identified as a SRC-associated tyrosine-phosphorylated protein in v-SRC-transformed cells [[30]]. FAK colocalizes with integrins at focal adhesions and is rapidly activated by autophosphorylation during integrin-mediated cell adhesion. The autophosphorylation site (Y397) and two proline-rich regions in FAK provide high-affinity binding sites for the SRC SH2 and SH3 domains, respectively [[31]]. Once bound, SRC phosphorylates two tyrosine residues in the FAK kinase domain to increase kinase activity. SRC also phosphorylates tyrosine residues in the C-terminal half of FAK that act as docking sites for other signaling molecules [[32]]. The absence of FAK or SRC impairs the function of the partner molecule. For example, fibronectin-induced cell migration is significantly reduced in cells lacking FAK, corresponding with reduced SRC activation [[33]]. Similarly, fibronectin-induced migration and FAK activation are reduced in cells with triple null mutations of *c-SRC*, *YES*, and *FYN* [[34]]. These findings show the importance of SFK-FAK interactions for normal intracellular signaling in response to extracellular matrix (ECM)-dependent stimulation.

4. Expression and function of individual SFKs within the CNS

Nine SFKs have been identified, eight of which are expressed in humans. Several SFKs have a distinct tissue distribution pattern. Those expressed in neural tissue are LYN, FYN, YRK (expressed in chickens only), LCK [[35]], and the ubiquitous SFKs c-SRC and YES [[23, 36]]. LYN appears to have a functional role in both embryonic and adult brain. In embryonic brain, oligodendrocyte progenitor proliferation requires LYN activation by integrin $\alpha_v\beta_3$ [[37]], LYN activity is also detected in normal adult brain [[38]]. Examination of *LYN* mRNA distribution during mouse brain development using in situ hybridization showed lower *LYN* expression in embryonic mouse brain relative to adult mouse brain, in which high levels of mRNA were detected in discrete regions [[39]]. LYN also plays an antiapoptotic role in the brain, protecting neurons from glutamate-related neurotoxicity through integrin signaling [[40, 41]]. FYN plays a role in brain development, demonstrated by studies showing that expression of FYN is necessary for oligodendrocyte maturation [[37, 42]] and synapse formation [[43]]. FYN is involved in promoting myelination [[44]] and may also play a role in Alzheimer's disease progression by disrupting tau protein-mediated microtubule stabilization [[45]]. In mouse studies, *LCK* expression has been detected in distinct brain regions including the hippocampus and cerebellum [[35]]. The above data suggest that individual SFKs likely have distinct functions within the CNS. This may depend in part on individual SFK expression levels and on whether there is co-temporal expression of proteins that activate individual SFK members (such as integrins or growth factor receptors).

5. Increased SRC activity in glioblastoma

Investigators have found elevated SRC activity in GBM compared with normal brain samples using both Western blotting for phosphorylated SRC and SRC kinase activity assays [[38]]. The increased SFK activity in GBM samples is largely (>90%) due to elevated LYN activity [[38]]. More recently, investigators have shown that SRC activity/phosphorylation was elevated in GBM samples and cancer cell lines, including T98G and U87, compared with normal tissue [[46]]. The increased SRC activity in GBM is not due to amplification or mutation of SFK genes, because the Cancer Genome Atlas Research Network reported no change in *SRC* mRNA expression, gene amplification, or mutation in GBM tumors [[47]]. This is consistent with several reports studying colorectal and rectal cancer, where no activating mutations, deletions or amplifications of *SRC* were found [[48-50]]. In a very small subset of colon cancers an activating mutation of c-SRC at codon 531 has been described; however, the presence of this mutation in the population studied (a Chinese population) did not correlate with an increased risk of developing colon cancer [[51, 52]]. Also, in certain leukemias there may be loss of SRC due to deletion of chromosome 20q [[53, 54]]. Thus, the increased SRC activity in GBMs is likely due to increased activation of cell surface growth factor receptors and integrins that activate SFKs.

6. Mechanisms of action of SFKs in tumor biology: evidence of a role for SRC in glioblastoma

Tumor growth is typically associated with one or more of the following: increased proliferation, reduced apoptosis, inhibition of autophagy, and increased angiogenesis. Also, invasion of primary tumors and metastasis involves altered cell adhesion processes, increased motility and increased protease expression. In addition, metastasis requires intravasation/extravasation of tumor cells and colonization of a site distant to the primary tumor [[55]]. Preclinical studies of cancer cells, including GBM cell lines, have shown that dysregulated SFK signaling plays a role in the above processes [[56-61]]. The role for SRC in GBM tumor development is supported by a study in transgenic mice expressing *v-SRC*. These mice spontaneously developed low-grade tumors that progressed to a morphology resembling human GBM (14% of mice at 65 weeks) [[62]].

6.1. Proliferation

SRC plays an important role in promoting tumor cell proliferation, as demonstrated by several breast cancer, prostate cancer, and GBM tumor models in which blockade of SRC activity inhibited proliferation [[63-67]]. In tumors, SRC mediates signaling from extracellular proteins known to promote proliferation, including growth factor receptors [[68, 69]] and integrins [[70]]. SRC activation leads to downstream signaling through the RAS/mitogen-activated protein kinase (MAPK) and PI3K pathways, which have known roles in promoting tumor proliferation, survival, and invasion (Fig. 1) [[71],[72, 73]]. In addition, *v-SRC* has been shown to stimulate proliferation by inducing cyclin expression [[74]]. SRC/FAK complexes can also activate RAS, as shown by promotion of anchorage-independent proliferation of *FAK*-overexpressing GBM cells and by the growth of GBM xenografts in the mouse brain [[75]]. This proliferation appears to be mediated by a combination of FAK-induced *KLF8* expression, cyclin D1 activation, and reduced expression of the cyclin-dependent kinase inhibitor p27 [[76]]. These data suggest that SRC-induced effects may involve FAK and that inhibition of SRC/FAK signaling may be effective in inhibiting tumor growth.

6.2. Apoptosis

Anoikis is a form of programmed cell death induced by detachment of adherent cells from the ECM [[77]]. For solid tumor cells to detach from the primary tumor and metastasize to a distant site, they must acquire anoikis resistance. There is evidence that several SFKs (c-SRC, LYN, FYN, YES, and LCK) activate antiapoptotic or prosurvival signal transduction pathways, including those mediated by PI3K and AKT signaling [[78-80]]. Dasatinib, a potent SFK inhibitor, induces apoptosis of certain adherent cancer cells, such as bone sarcoma cells, potentially by inhibiting the FAK/p130CAS pro-survival pathway [[81]]. Although further preclinical studies are needed to clarify the role of SFKs in anoikis and apoptosis resistance, it is feasible that SFK inhibitors may potentially promote anoikis or apoptosis, thereby protecting against metastasis.

6.3. Autophagy

Recently, Milano and coworkers [[82]] showed that dasatinib inhibited in vitro GBM cell growth by inducing autophagic cell death. This was enhanced in cells expressing functional phosphatase and tensin homolog deleted on chromosome 10 (PTEN) gene and when dasatinib was combined with TMZ. Combining dasatinib with carboplatin or irinotecan (agents thought to be pro-apoptotic) did not significantly increase autophagic cell death in most GBM cell lines [[82]]. Because autophagic cell death results in caspase activation, this type of cell death may have contributed to inhibition of cell growth or induction of apoptosis observed in earlier studies of SFK inhibitors in cancer cells.

6.4. Altered cell adhesion and motility/migration

During solid tumor development, reduced cell-cell adhesion and increased turnover of cell-ECM contacts can contribute to tumor cell migration and metastasis. SFK signaling is necessary for cell adhesion, but SFKs can also disrupt cell-cell adhesion, thereby promoting tumor cell invasion. SRC-mediated decreases in cellular adhesiveness result from multiple mechanisms, including redistribution of focal adhesion component proteins [[83, 84]], altered regulation of integrin signaling, and decreased deposition of ECM proteins [[85, 86]]. For example, in epidermoid squamous carcinomas, FYN activation was essential for EGF-dependent hemidesmosome disassembly and tumor invasion [[87]]. Hemidesmosome formation required integrin $\alpha_6\beta_4$. In U87 GBM cells stimulated with PDGF-BB, LYN and FYN were differentially activated and had different intracellular associations with integrins. LYN, but not FYN, was specifically activated when integrin $\alpha_v\beta_3$ was engaged and was required for cell migration on vitronectin [[88]]. Thus, context-dependent growth factor receptor signaling (dependent on the integrin engaged and the SFK expressed) can determine whether there is cell-ECM or cell-cell adhesion.

In tumor cell models, including GBM, treatment with a SRC/SFK inhibitor or short interfering RNA blocked tumor cell invasion and migration [[46, 59, 67, 82, 88-90]]. A recent study has examined the mechanisms behind GBM cell migration induced by mutation or loss of PTEN protein, which occurs in 60-70% of GBMs. Stable overexpression of CSK or treatment with the laboratory SFK inhibitor PP1 inhibited vitronectin-stimulated transwell migration of U87MG and U373MG GBM cells. FYN was specifically shown to promote vitronectin-stimulated migration induced by loss of PTEN expression [[91]]. Interestingly, in a separate study, human GBM cells with functional PTEN showed increased sensitivity to growth inhibition by dasatinib compared with cells with low PTEN expression levels [[82]]. Inhibition of in vitro invasion was also observed.

6.5. Intravasation, extravasation, and invasion

GBM tumors rarely metastasize outside of the CNS, possibly due to a combination of the blood-brain barrier's (BBB) resistance to intravasation and a lack of suitable cell adhesion molecules on the surface of GBM cells to facilitate homing to target tissues [[92]]. However, GBM tumors are characterized by diffuse local invasion, which involves processes shared with metastasis, including increased motility, altered adhesion, and remodeling of ECM. Invasive tumor cells are probably one of the major factors in GBM recurrence following surgery, radiotherapy, and chemotherapy.

The importance of SFKs in local invasion has been demonstrated in mouse intracerebral xenograft models. GBM invasion was significantly decreased in *SRC* knockout mice compared with control mice, suggesting that *SRC* expression by normal brain tissue is required for invasion/infiltration of GBM cells [[61]]. It has been suggested that VEGF may increase vascular permeability in normal mice by increasing *SRC* activity; therefore VEGF inhibitors should reduce invasiveness. However, VEGF inhibitors have been shown to cause changes in tumors that are associated with increased infiltrative activity [[93]]. This indicates that direct inhibition of *SRC* activity may be a more direct method of blocking GBM invasion than VEGF inhibition. In a primary human GBM xenograft model, increased *SRC*- and *PI3* kinase-dependent invasiveness in response to bevacizumab has been observed, which was prevented by dasatinib [[94]]. *SRC* inhibition may also inhibit invasion by disrupting crosstalk between *SRC* and *FAK*, because *FAK* activation promotes GBM invasion through downstream signaling molecules such as human enhancer of filamentation 1 (*HEF1*), a *p130CAS* family member [[95]].

In vitro studies have shown that *SRC* regulates formation of invadopodia -specialized actin-rich membrane protrusions that degrade ECM [[63, 96, 97]]. Laboratory SFK inhibitors PP2 and SU6656, dominant-negative *SRC*, and *CSK* all significantly inhibit GBM cell invasion in vitro, with a corresponding loss of actin in invadopodia [[98]].

Matrix metallo-proteases (MMPs) have a well-established role in tumor invasion [[99]]. *SRC*-dependent expression of membrane-bound and secreted MMPs has been demonstrated in models of cancer cell invasion including GBM tumors [[60, 100-102]]. In T98G and NCH125 GBM cells stimulated by CD95 activation, YES signaling mediated upregulated MMP expression and increased invasion [[58]].

Intravasation and extravasation enable systemic cancers to metastasize to the CNS. *SRC*-mediated extravasation may be particularly important for tumors that metastasize to the brain. In vitro studies of gastric and colorectal cancer cells have shown that *SRC* signaling is involved in intravasation through its role in the upregulated expression of chemokine receptors (*CXCR1* and *CXCR2*) and the urokinase receptor [[103, 104]]. *SRC* activity can also affect extravasation through its downstream role in VEGF signaling pathways. Disruption of vascular endothelial cell-cell junctions following VEGF-activated *SRC* signaling increases vascular permeability, permitting tumor cell extravasation [[105, 106]]. At the BBB, angiogenesis and tight junction formation are regulated by *SRC*-suppressed C-kinase substrate (*SSECKS*), a protein that decreases expression of VEGF and increases expression of angiopoietin-1, an antipermeability factor [[107]]. Decreased *SSECKS* activity caused by increased *SRC* activity could potentially enhance vascular permeability facilitating metastasis to the brain.

6.6. Angiogenesis

Angiogenesis is critical for establishment and growth of solid tumors and is a key feature of GBM. As discussed previously, the antiangiogenic agent bevacizumab increases short-term PFS in patients with recurrent GBM. Because *SRC* can induce VEGF expression, SFKs

have a potential role in the angiogenic process [[108]]. This is supported by studies of GBM-like tumors that develop in transgenic *v-SRC*-expressing mice, in which expression of VEGF and other proangiogenic factors was observed at early stages of tumor development [[109]]. In addition, in human solid tumor cell lines, SRC inhibition reduces VEGF expression, thereby decreasing proangiogenic activity [[110]].

Because of their role in mediating VEGF receptor signaling, c-SRC and YES are required for VEGF-induced angiogenesis seen in mouse studies [[111]]. The potential additive effects of combining SFK inhibitors with antiangiogenic agents are being explored in clinical trials.

6.7. SFKs may be activated by irradiation

An in vitro study in PTEN-mutated glioma cells found that exposure to ionizing radiation activated SRC, in turn activating EGFR, p38 MAP kinase/AKT, and PI3K/AKT signaling pathways, and increasing MMP2 expression and cell invasiveness [[60]]. Therefore, SRC inhibitors should inhibit SRC-dependent increases in invasion following radiotherapy. In preclinical studies, saracatinib, an inhibitor of SFKs, BCR-ABL, KIT, PDGFR α/β , and VEGFR2 kinases, increased radiosensitivity of lung cancer cells [[112, 113]]. In addition, SU6656 in combination with radiotherapy decreased human umbilical vein endothelial cell survival in vitro compared with radiation alone. These observations were corroborated by an in vivo study showing that SU6656 administered prior to irradiation significantly enhanced radiation-induced destruction of tumor-associated blood vessels, and delayed tumor growth of Lewis lung carcinoma models [[114]].

7. SRC activation in brain metastases from solid tumors

Brain metastases are a frequent complication of solid tumors and may arise several years after removal of the primary tumor. As discussed, SRC has a key role in metastasis, suggesting that increased SRC activity could increase the likelihood of brain metastasis. SRC inhibitors may potentially prevent implantation of cancer cells from outside the brain or prevent growth of dormant brain metastases arising from primary tumors with elevated SFK activity.

Breast cancer is one of the most common causes of brain metastases. A study of gene expression signatures found increased expression of components of the SRC signaling pathway in 60% of breast cancer metastases to bone and in 25% of breast cancer metastases to the brain [[115]]. Patients with HER2-positive breast cancer have an increased risk of brain metastases [[116, 117]]. Although no direct role for SRC in brain targeting by HER2-positive metastatic breast cancer cells has been demonstrated, HER2 could potentially promote metastasis through direct phosphorylation of SRC [[118]] or other processes involving SRC, such as disruption of vascular endothelial integrity [[119]] or upregulation of urokinase-type plasminogen activator receptor, a proinvasive factor [[120, 121]].

Studies of melanoma and melanocyte cell lines have shown that neurotrophin and nerve growth factor (NGF) signaling elevated protein levels and activity of YES, with no effect on SRC activity. The degree of YES activation correlated with the invasive potential of melanoma cell lines, suggesting that upregulated YES expression or activity may contribute to the brain-metastatic phenotype [[122]].

In addition to a potential role in metastasis to brain, the antiproliferative activity of SRC inhibitors against primary tumors, including breast cancer, lung cancer, and melanoma, suggests that these agents may also have some activity against brain metastases derived from these tumors [[123-125]].

8. Preclinical studies of SRC inhibitors in glioblastoma

Dasatinib

Dasatinib is a potent inhibitor of c-SRC and other SFKs such as LYN and FYN, and also has activity against BCR-ABL, KIT, PDGFR α/β , and EPHA2 [[126, 127]]. The effects of dasatinib on GBM have been investigated in several preclinical studies. In a recent study, dasatinib decreased viability in 13/22 GBM cell lines (effector concentration for halfmaximum response (EC₅₀) of <1 μ M). Dasatinib also induced apoptosis in three GBM lines and inhibited cell migration (EC₅₀ <500 nM) in 14/22 GBM cell lines. Site-directed mutation of potential kinase targets for dasatinib confirmed that SRC inhibition mediated the effects of dasatinib in GBM cells [[46]]. In addition, dasatinib was more effective in blocking in vitro glioma cell proliferation combined with TMZ [[82]].

PP2

Inhibition of proliferation by PP2, a laboratory SFK inhibitor, has been demonstrated in the U373MG human GBM cell line [[128]]. PP2 also inhibited GBM cell migration stimulated by phorbol 12-myristate 13-acetate-induced cytoskeletal reorganization, and decreased formation of CAS/CRK/RAC complexes that associate with focal adhesions to promote cell migration [[59]].

SU6656

SU6656 is a small-molecule inhibitor of SRC, FYN, YES, and LYN that inhibits PDGF-stimulated DNA synthesis and cell growth in U251 glioma cells and invasion of glioma cell line spheroids implanted in collagen type I matrices [[98]]. Effects on invasion appeared to be mediated by a rapid change in actin dynamics, similar to effects seen in PP2-treated cells. SU6656 also enhanced in vivo radiation-induced apoptosis and destruction of vascular endothelium, suggesting potential use of SFK inhibitors as radiosensitizers [[129]].

Bosutinib and saracatinib

Although other SFK inhibitors, including bosutinib (SKI-606) [[130]] and saracatinib (AZD0530) [[131]] have been investigated in solid tumors, data have not been published using GBM cells or in vivo models.

9. Potential for resistance to SRC inhibitors

Using a targeted therapy to inhibit a heterogenous population of tumor cells applies a selective pressure that could lead to development of treatment resistance. Although studies have not been performed in GBM, a recently published breast cancer xenograft study reported that estrogen receptor-positive tumors developed resistance to saracatinib monotherapy by activating alternative signaling pathways, including MEK and PI3K/AKT/mammalian target of rapamycin signaling [[132]]. In this study, resistance was overcome by combining saracatinib with the aromatase inhibitor letrozole, thus providing another reason to investigate combination therapy with SRC inhibitors and other classes of drugs.

In addition to potently inhibiting SFKs, dasatinib also inhibits BCR-ABL, a chimeric kinase formed during the development of chronic myeloid leukemia (CML). During dasatinib treatment of patients with CML, *BCR-ABL* point mutations have been associated with dasatinib resistance [[133]] and specific mutations detected in clinical samples from resistant patients correlated with preclinical mutagenesis studies [[134]]. The potential of *BCR-ABL* to develop resistance mutations is thought to be due predominantly to genomic instability resulting from BCR-ABL kinase activity [[135]]. No preclinical studies have been

performed to determine if SFKs have the potential to develop mutations during SRC inhibitor treatment, although this would be an interesting area for future investigation.

10. Clinical trials of SRC inhibitors in glioblastoma

Despite decades of research, no therapy has been shown to block the invasive tumor phenotype that makes glioblastoma so difficult to treat. The preclinical data discussed above provide strong support for the hypothesis that SRC/SFK inhibition may be a promising strategy to inhibit GBM invasion into normal brain. Among the SRC inhibitors that are in clinical trials for solid tumors, only dasatinib is currently being assessed as a therapy for GBM.

Five ongoing trials are investigating dasatinib as a treatment for newly diagnosed and recurrent GBM in adults, either as a monotherapy or in combination with other agents/radiotherapy. In a current phase II clinical study, patients with recurrent GBM or gliosarcoma (NCT00423735) received dasatinib monotherapy and preliminary evidence of activity was reported in a small number of patients; further optimization of dasatinib dosing is ongoing via intra-patient dose escalation [[136]]. Additional studies are evaluating dasatinib-based combination therapy for recurrent GBM, including a phase I trial evaluating dasatinib plus the EGFR inhibitor erlotinib (NCT00609999) and a randomized phase II trial of lomustine alone versus lomustine plus dasatinib (NCT00948389). A phase I/II study in patients with newly diagnosed glioblastoma is evaluating the efficacy of dasatinib combined with radiotherapy and concomitant TMZ, followed by adjuvant treatment with dasatinib plus TMZ (NCT00895960). All of these studies are currently recruiting patients and have yet to publish data in peer-reviewed journals (Table 1).

When investigating novel agents for treating CNS tumors, the issue of BBB penetration must be considered. A preclinical study showed that dasatinib crossed the BBB and reduced intracranial leukemia xenograft volume [[137]]. These investigators also reported clinical activity of dasatinib in 11 patients with CNS metastases of Philadelphia chromosome-positive leukemia, suggesting that dasatinib and perhaps other small-molecule SFK inhibitors can cross the BBB to exert a clinical effect.

11. Unanswered questions

In vitro data have shown that SFKs and FAK have a close relationship during several normal and oncogenic cellular activities, which may be of increased relevance in GBM. This raises the question of what happens to FAK activity when SFKs are inhibited, and whether the antitumor activity seen with SFK inhibitors is partly due to a decrease in FAK activity. Also, the effect of SFK inhibitors on the interactions between SFKs and the FAK family member PYK2 requires further investigation.

As discussed above, SFK activity is significantly elevated in de novo GBM tumors [[38]]; however, it is not known if SFK activity is elevated in secondary GBM tumors arising from lower-grade gliomas. This is an important consideration because different genetic alterations and tyrosine kinase activities are detected in these two types of GBM. The development of molecular probes to quantify different SFK activities in complex tissue sections would be beneficial to further studies in this area.

Finally, the concept that anti-VEGF therapy-induced invasion may be blocked by SRC inhibition raises several unanswered questions. First, it is not known if increased invasion during antiangiogenic therapy is due to overexpression or activation of SRC/SFKs. Secondly, if SRC/SFKs mediate this invasive phenotype, it is not known if delivery of small molecule targeted agents will be reduced following the reduction in vascular permeability

seen with antiangiogenic therapy. Ongoing preclinical and clinical studies will attempt to answer these important questions.

12. Conclusions

Because of the key role of SFKs in tumor development and oncogenic signal transduction, SFKs are clearly a rational target for GBM treatment. This hypothesis is supported by preclinical evidence demonstrating that increased SRC or SFK activity is associated with GBM proliferation and invasion. Preclinical data show that SFK-targeting agents have single-agent activity and that combining dasatinib with TMZ has increased activity compared with TMZ alone [[82]]. In addition, preliminary evidence suggests that SFK inhibition may increase tumor cell sensitivity to radiation, which could have direct relevance for radiotherapy of both GBM and brain metastases. Preliminary results from clinical trials of dasatinib will provide the first indication of whether SFK inhibitors have the potential to become a new class of therapy for GBM. In addition to a possible role in GBM there is considerable evidence of the role of SFKs during metastasis. Therefore, solid tumors with aberrant SFK expression or activity may have an increased potential for migration into the brain from primary sites outside the CNS or growth of a previously undetectable dormant micrometastasis. This provides a further area of investigation for SFK inhibitors that is also relevant to CNS tumors.

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Fig. 1.

Contribution of SRC-mediated pathways to tumor progression. In tumor cells, interaction of SRC-family kinases (SFKs) with receptor tyrosine kinases (RTK), integrins, or focal adhesion kinase (FAK) activates the kinase activity of SFKs. SFKs activate downstream signaling pathways that mediate proliferation (green), angiogenesis (red), survival (blue), and motility/migration (orange). Cyclin D1 can be activated by v-SRC. RTK, receptor tyrosine kinase; FAK, focal adhesion kinase; MAPK, mitogen activated protein kinase; VEGF, vascular endothelial growth factor; JAK, Janus kinase; STAT, signal transducers and activators of transcription; IL, interleukin; PI3K, phosphatidylinositol 3-kinase; NFκB, nuclear factor kappa B; IKK, inhibitor of kappa-B kinase; Shc, SRC transforming protein; GRB2, growth factor receptor-bound protein 2; SOS, son-of-sevenless; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; MLCK, myosin light chain kinase; CAS, Crk-associated substrate; JNK, Jun N-terminal Kinase; RhoGAP, Rho GTPase activating protein.

Table 1

Ongoing clinical trials of dasatinib in glioblastoma

ClinicalTrials.gov identifier	Agent(s)	Phase	Disease stage	Primary endpoints	Estimated enrolment	Sponsor
NCT00895960	Dasatinib + RT/TMZ	1/2	Newly diagnosed	• Maximum tolerated dose	72	MDACC
NCT00609999	Dasatinib + erlotinib	1	Recurrent	• Maximum tolerated dose • Dose-limiting toxicity	48	Duke University
NCT00423735	Dasatinib	2	Recurrent	• Progression-free survival at 6 months	113	RTOG
NCT00948389	Dasatinib + lomustine	2	Recurrent	• Hematologic and nonhematologic toxicity • Proportion of patients disease free by MRI	108	Bristol-Myers Squibb European Organization for Research and Treatment of Cancer

RT, radiotherapy; TMZ, temozolomide; MDACC, MD Anderson Cancer Center; NCCTG, North Central Cancer Treatment Group; RTOG, Radiation Therapy Oncology Group.