Noninvasive Imaging of $\alpha_{v}\beta_{3}$ Function as a Predictor of the Antimigratory and Antiproliferative Effects of Dasatinib

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Abstract

Src family kinases (SFKs) are commonly deregulated in cancer cells. Among other functions, SFKs are critical for cellular migration and invasion. SFK inhibitors are being studied as targeted cancer drugs, but there are no biomarkers for noninvasive assessment of SFK inhibition. The aim of this study was to evaluate whether imaging of $\alpha_{v}\beta_{3}$ integrin activity with positron emission tomography (PET) and $[^{64}\text{Cu}]$DOTA-cyclo-(Arg-Gly-Asp-DPhe-Lys) $[^{64}\text{Cu}]$DOTA-c(RGDfK) may provide a sensitive means of monitoring tumor activity with PET. In parallel, fluorodeoxyglucose (FDG) scans were performed to assess tumor metabolism in response to dasatinib treatment. Dasatinib significantly ($P < 0.0001$) reduced $[^{64}\text{Cu}]$DOTA-c(RGDfK) uptake by up to 59% in U87MG xenografts [2.10 ± 0.14% ID/g in the 95 mg/kg group and 3.12 ± 0.18% ID/g in the 72 mg/kg group, versus 5.08 ± 0.80% ID/g in controls]. In contrast, tumor FDG uptake showed no significant reduction with dasatinib therapy (8.13 ± 0.45% ID/g in treated versus 10.39 ± 0.41% ID/g in controls; $P = 0.170$). Histologically, tumors were viable at the time of the follow-up PET scan but showed inhibition of focal adhesion kinase. Continued dasatinib treatment resulted in a significant inhibition of tumor growth (tumor size on day 10 of therapy: 21.13 ± 2.60 mm² in treated animals versus 122.50 ± 17.68 mm² in controls; $P = 0.001$). $[^{64}\text{Cu}]$DOTA-c(RGDfK) may provide a sensitive means of monitoring tumor response to SFK inhibition in $\alpha_{v}\beta_{3}$-expressing cancers early in the course of therapy. [Cancer Res 2009;69(7):3173–9]

Introduction

Molecurally targeted therapies are becoming increasingly important in the treatment of cancer, as the signaling mechanisms underlying malignancy are elucidated. Whereas some small-molecule inhibitors are effective in a large percentage of patients, as is the case with imatinib in the treatment of chronic myeloid leukemia, most targeted therapies are clinically effective in a limited subset of patients with common solid tumors (e.g., erlotinib in non–small cell lung cancer; ref. 1). In addition, tumors that initially respond frequently proceed to develop resistance to targeted therapy. Therefore, identifying new therapeutic agents and a means by which to predict and monitor treatment response are compelling priorities in the field of oncology.

Inhibition of platelet-derived growth factor receptor (PDGFr) and Src family kinases (SFKs) is a promising anticancer strategy, as both oncopogenes are up-regulated and important in the pathogenesis of various malignancies, including glioblastoma multiforme (GBM), soft tissue sarcoma, gastrointestinal cancer, pancreatic cancer, and melanoma (2–5). Preclinical studies have shown that inhibition of PDGFr can inhibit growth and reduce the invasiveness of tumor cells, effects that are mediated through activation of SFKs (6, 7). These studies support the clinical testing of dasatinib, an inhibitor of SFKs (and other tyrosine kinases) in solid tumors, and clinical trials have recently started in glioblastoma, pancreatic adenocarcinoma, breast cancer, and non–small cell lung cancer. Such trials would benefit from noninvasive techniques to monitor the molecular changes in response to dasatinib therapy.

Positron emission tomography (PET) is a valuable tool for identifying the molecular changes following therapeutic interventions in patients. For monitoring effects of SFK inhibitors in patients, PET probes binding to the $\alpha_{v}\beta_{3}$ integrin are of particular interest. The integrin $\alpha_{v}\beta_{3}$ is a cellular adhesion molecule that is frequently expressed on malignant tumors and acts as an important receptor affecting tumor growth, local invasiveness, and metastatic potential (8). SFK activity is necessary for localization of $\alpha_{v}\beta_{3}$ to focal adhesions and integrin-mediated migration and invasion (7).

For imaging of the $\alpha_{v}\beta_{3}$ integrin, cyclic pentapeptides containing the tripeptide sequence arginine-glycine-aspartate (RGD) have been developed. These peptides specifically bind to $\alpha_{v}\beta_{3}$ in its activated state but not to related integrins such as $\alpha_{IIb}\beta_{3}$ (9, 10). Recent clinical trials have shown that PET imaging with radiolabeled RGD peptides allows quantitative expression of activated $\alpha_{v}\beta_{3}$ integrin in patients with various malignant tumors (10, 11).

Based on these data, we hypothesized that PET imaging with radiolabeled RGD peptides may provide a noninvasive readout for the anti-invasive effects of SFK inhibition. As a model to test this hypothesis, we used U87MG, a GBM cell line with high expression of $\alpha_{v}\beta_{3}$ in which PDGFr inhibition has a significant antimigratory effect in a SFK-dependent manner (7). We show evidence that dasatinib alters invasion of glioblastoma cells and we show that the radiolabeled RGD peptide $[^{64}\text{Cu}]$DOTA-c(RGDfK) can be used to monitor treatment response to dasatinib in vivo.
Materials and Methods

Cell culture. The glioma cell line U87MG was purchased from the American Type Culture Collection and cultured in DMEM (Invitrogen) supplemented with 10% fetal bovine serum (Omega Scientific), 2 mg/mL glucose, 100 units/mL penicillin, and 100 units/mL streptomycin (Invitrogen). Cells were grown at 37°C in an atmosphere of 5% CO2.

Invasion assay. To assess the effect of dasatinib on cell motility, a two-dimensional invasion assay was performed using six-well Transwell polycarbonate membrane inserts with 8.0-μm pores (Costar) coated from the bottom with 25 μg/mL fibronectin (Chemicon) as an extracellular matrix barrier. After adding serum-free MEM to the lower compartments, 5 × 10^5 U87MG cells in serum-free MEM/bovine serum albumin (5 mg/mL) were seeded onto the upper chambers and incubated for 6 h at 37°C, 5% CO2. For pharmacologic inhibition, dasatinib (Bristol-Myers Squibb Oncology) or c(RGDfK) (Peptides International) was added to cells in the upper chamber at the designated concentrations at the time of plating. DMSO was used as a vehicle control and to dilute the 20 mM stock dasatinib. After 6 h, noninvasive cells on the upper surface were removed with cotton swabs, and the remaining invaded cells on the lower surface were fixed in 4% paraformaldehyde and stained with 0.25% cresylviolet. The number of invasive cells was calculated using pictures of six random fields with magnification and then calculating the area in each photomicrograph according to the manufacturer's instructions and imaged with an Olympus BX61 microscope. The peptide DOTA-c(RGDfK) was synthesized as described previously (13). Labeling with copper-64 chloride (MDS Nordion) was performed by incubating 1.25 μg DOTA-c(RGDfK) with 37 MBq ⁶⁴Cu for 1 h at 50°C in a total volume of 200 μL of 0.1 mol/L ammonium acetate at pH 7.1. Purification of the radiolabeled peptide was performed using a 1-mL Strata-X 33-μm polymeric reversed-phase column (Phenomenex, Inc.). Following a water wash, the labeled peptide was eluted in 100% ethanol, dried over argon gas at 60°C, and resuspended in 0.9% saline. All labeling solutions were pretreated with Chelex-100 (Bio-Rad) at 1.2 g/L. Labeling efficiency ranged from 75% to 85% for a specific activity of the radiolabeled peptide of 22.2 to 25.6 GBq/mg. Thus, the amount of peptide injected ranged between 0.74 and 0.83 μg.

Xenograft model and dasatinib treatment. Severe combined immune-deficient mice were purchased from The Jackson Laboratory. All animal manipulations were performed with sterile technique following the guidelines of the University of California at Los Angeles (UCLA) Animal Research Committee. U87MG (2 × 10^6 cells per mouse) were resuspended in PBS and Matrigel (BD Biosciences) and injected s.c. at the right shoulder of 7-wk-old male mice. After tumors had grown to an approximate size of 6 mm, groups of three to five animals were gavaged daily with vehicle (1:1, propylene glycol/water) and 72 or 95 mg/kg of dasatinib. Tumor length and width were measured over a 10-d period with calipers.

Micro-PE/T-computed tomography imaging. Sixty-minute dynamic micro-PE/computed tomography (CT) scans were obtained with 15 to 20 MBq (peptide mass: 0.74–0.83 μg) ⁶⁴CuDOTA-c(RGDfK) injected via tail vein after 72 h of dasatinib treatment using a micro-PE FOCUS 220 PET scanner (Siemens) and a MicroCAT II CT scanner (Siemens; ref. 14). Fifteen hours later, animals underwent another micro-PE/CT study (10-min static imaging, magnification, >40).
emission, 7-min micro-CT scan; refs. 15, 16). PET images were reconstructed by filtered back projection using a ramp filter to yield an image resolution of 1.7 mm (17). In a separate experiment, static emission $^{[18F]}$Fluorodeoxyglucose (FDG) micro-PET/CT scans were performed with 7 to 10 MBq FDG (mass, <0.1 μg) after 1-h uptake in animals treated for 72 h with dasatinib or vehicle control.

**Image analysis.** To determine tracer concentration in various tissues, ellipsoid regions of interest were placed in the region that exhibited the highest radioactivity as determined by visual inspection on fused micro-PET/CT images generated by the AMIDE software (18). Tracer uptake in the highest radioactivity as determined by visual inspection on fused micro-PET/CT images generated by the AMIDE software (18). Tracer uptake in the xenograft tumors and normal tissues are expressed as percent of the decay-corrected injected activity per cm$^3$ of tissue (percentage injected dose/gram (%ID/g)). Previous studies have shown that uptake of $^{[64Cu]}$DOTA-c(RGDfK) correlates closely with the expression of activated αvβ3 integrin (19).

**Immunohistochemistry.** Following anesthetization and sacrifice of mice, tumors were removed and frozen in liquid nitrogen. Frozen tumor tissues were sectioned (6 μm) and stained with H&E following standard protocols or immunohistochemically stained with primary antibodies against CD31 (BD Pharmingen), phospho-FAK (Y861), and αvβ3 (Chemicon) followed by biotinylated secondary antibodies and avidin-biotin complex (Vector Laboratories). Visualization of all staining was performed with NovoRed substrate (Vector Laboratories) and tissues were counterstained with hematoxylin. Images were generated with an Olympus BX61 microscope.

**Statistical analysis.** Quantitative results are expressed as mean ± SD. Comparisons were made by $t$ tests or by ANOVA as appropriate (GraphPad Prism, GraphPad Software). Differences were considered significant when P < 0.05.

**Results**

**U87 invasion is dependent on αvβ3 function and is inhibited by dasatinib.** U87MG cells plated in fibronectin-coated Boyden chambers and treated with 50 or 100 nmol/L of dasatinib for 6 hours showed a significant reduction in invasion compared with control (40.30 ± 7.86% and 15.36 ± 5.70% of control, respectively; P < 0.001; Fig. 1A and B). To determine the importance of αvβ3 function in U87MG invasion, cells were treated with 2 mmol/L c(RGDfK) peptide to effectively saturate all available functional binding sites (20). This inhibited the ability of U87MG to invade through fibronectin to 11.48 ± 3.35% of controls (P < 0.001; Fig. 1A and B). A similar reduction in invasiveness was observed when cells were grown on collagen, which is not a ligand of the αvβ3 integrin.

**Dasatinib inhibits phosphorylation of SFKs and FAK and impairs the formation of focal adhesions.** Cell lysates prepared for Western blot following 6 hours of 100 nmol/L dasatinib treatment showed target inhibition of SFK phosphorylation at activation site Tyr$^{416}$ and FAK at Tyr$^{861}$ phosphorylation, a SFK-dependent activation site. A decrease was also seen in FAK Tyr$^{397}$, an integrin-dependent autophosphorylation site (Fig. 2A).

Immunofluorescence was used to study the effect of SFK/FAK inhibition on the formation of focal adhesion complexes in U87 cells on a fibronectin surface. Staining for dimerized αvβ3 showed the integrin localized on the cell surface in numerous focal adhesions in control U87MG cells (Fig. 2B). Following 6 hours of 100 nmol/L dasatinib treatment, cell morphology was notably altered as seen in the images and αvβ3 was no longer clustered in focal adhesion complexes (Fig. 2B). By 6 hours, the ability of the cells to remain attached to the fibronectin surface was so impaired that there were insufficient numbers of attached cells remaining on the slides to stain. Total levels of dimerized cell surface αvβ3 protein level following 6 or 24 hours of 100 nmol/L dasatinib did not change relative to control as assessed by FACS, nor did total β3

![Image 1](https://example.com/image1.png)

**Figure 2.** A. Western blot of U87MG cell lysates shows target inhibition of SFKs and FAK with 6 h of 100 nmol/L dasatinib treatment. B. decreased formation of focal contacts in U87MG cells treated with 100 nmol/L dasatinib for 6 h as shown by immunofluorescent staining of dimerized αvβ3 integrin. Magnification, ×200. Cell surface αvβ3 levels on FACS (C) and total β3 protein levels on Western blots (D) do not change with 24 h of 100 nmol/L dasatinib treatment. FACS samples performed in duplicate.
levels decrease in a Western blot of corresponding cell lysates (Fig. 2C and D, 6-hour data not shown).

Dasatinib decreases uptake of $[^{64}\text{Cu}]$DOTA-c(RGDfK) in U87MG xenografts and markedly inhibits tumor growth. Dasatinib treatment significantly reduced $[^{64}\text{Cu}]$DOTA-c(RGDfK) uptake by 39% in the 72 mg/kg dose group and 59% in the 95 mg/kg dose group after 72 hours of treatment ($2.10 \pm 0.14\% \text{ID/g, } n = 3, \text{ in } 95 \text{ mg/kg}; 3.12 \pm 0.18\% \text{ID/g, } n = 4, \text{ in } 72 \text{ mg/kg}; 5.08 \pm 0.80\% \text{ID/g, } n = 7, \text{ in controls})$ as shown in Fig. 3A and B ($P < 0.0001$, one-way ANOVA). Tumor-to-muscle and tumor-to-blood ratios showed similar changes with dasatinib therapy (Fig. 3C and D). The effect of dasatinib on tracer kinetics in the tumor and normal organs were examined with dynamic PET scans, which showed that tracer distribution and organ uptake were virtually identical between treated and untreated animals except in the U87 xenografts (Fig. 4).

In contrast to the RGD peptide tracer, there was no significant change in FDG uptake with 72 hours of 95 mg/kg dasatinib treatment ($P = 0.1704$; Fig. 5A), indicating that the tumor cells remained viable during dasatinib treatment.

U87MG tumor growth was markedly inhibited with continued dasatinib treatment, resulting in a 6-fold difference in tumor size between control (122.50 $\pm$ 17.68 mm$^2$) and treated animals (21.13 $\pm$ 12.60 mm$^2$) after 10 consecutive days of treatment ($P = 0.0011$, $t$ test). However, at the time of PET imaging, no appreciable difference in tumor size was present ($P = 0.1272$; Fig. 5B).

Discussion

In this study, we show that dasatinib treatment of human glioblastoma xenografts causes a rapid decrease in the uptake of the radiolabeled $\alpha_v\beta_3$ ligand $[^{64}\text{Cu}]$DOTA-c(RGDfK). In contrast, imaging of tumor glucose metabolism with FDG-PET did not reveal significant differences between animals treated with vehicle or dasatinib, although tumor growth was markedly inhibited by dasatinib therapy after 10 days of treatment. These findings suggest that PET with $[^{64}\text{Cu}]$DOTA-c(RGDfK) may represent a useful biomarker for monitoring noninvasively the cytostatic effects of dasatinib therapy.

Others have previously reported that dasatinib inhibits in vitro invasion in a variety of solid tumor types at nanomolar concentrations, confirming that invasion is commonly mediated through the activity of SFKs in malignant cells (21, 22). Our in vivo
data showing a significant loss of invasiveness after treatment with 50 nmol/L dasatinib show that this is also the case in the U87MG glioma cell line. Furthermore, our in vitro data indicate that U87MG relies heavily on the interaction between $\alpha_v\beta_3$ and specific substrates, such as fibronectin, for invasion in a two-dimensional invasion model. When integrin binding sites were saturated with an excess of c(RGDfK), or when $\alpha_v\beta_3$ binding substrate was absent as on a collagen surface, in vitro invasion of U87MG cells was greatly reduced.

Our in vitro and in vivo data suggest that dasatinib exerts its anti-invasive effect in U87MG through an inhibition of focal contact formation and loss of integrin activation that occur following impairment of SFK and FAK activation. The $\alpha_v\beta_3$ integrin exists in two states: an active state that bind ligands, such as the extracellular matrix proteins fibrinogen and fibronectin, and an inactive state that has a much lower affinity for these proteins and peptides (23, 24). Integrin activation also affects binding of synthetic ligands, such as cyclic RGD peptides (24). When integrins are mobilized to the cell surface and become activated, they group in clusters known as focal adhesions with a variety of other intracellular proteins. Focal adhesions form the interface between the extracellular matrix, cell surface integrins, and the cytoskeleton. These dynamic groups of structural and regulatory proteins also transduce external signals to the cell interior (24). The effect of SFKs on integrin-dependent invasion is mediated through FAK, which recruits other focal contact proteins or their regulators that dictate the assembly or disassembly of focal contacts and lead to cell migration (25, 26).

In our in vitro experiments, dasatinib inhibited SFKs and FAK at nanomolar concentrations. Furthermore, cell surface distribution of the $\alpha_v\beta_3$ integrin was drastically changed with dasatinib treatment. Whereas in untreated cells the $\alpha_v\beta_3$ integrin was clustered in focal adhesions, the cell surface stained much more diffusely for the $\alpha_v\beta_3$ integrin following dasatinib therapy. In

Figure 4. Time activity curves for different organs from dynamic micro-PET scans following injection of $^{64}$Cu-DOTA-c(RGDfK) in animals treated for 72 h with vehicle control (square) or 95 mg/kg dasatinib (triangle). The last time point represents data from 10-min static micro-PET scans performed 15 h following tracer injection. With the exception of the xenograft U87 tumor, there is no appreciable difference in tracer uptake in tissues of animals treated with dasatinib compared with control.
In contrast, dasatinib did not measurably affect the total protein levels of the αvβ3 integrin or the amount of the αvβ3 integrin on the cell surface. Thus, alterations in integrin clustering and activation, as opposed to a decrease in protein levels, seem to be the result of SFK/FAK inhibition.

Our in vivo data are also consistent with the hypothesis that dasatinib interferes with integrin activation and thereby reduces uptake of [64Cu]DOTA-c(RGDfK). The at time of PET imaging, treated xenografts were identical in size to vehicle-treated tumors and there was no evidence for treatment-induced necrosis on histopathologic analysis. Moreover, a significant reduction in the tumor vasculature or integrin expression was not observed. Thus, the drastically reduced uptake of [64Cu]DOTA-c(RGDfK) in treated xenografts cannot be explained by tumor cell death, a reduction in tumor perfusion, or a reduction in integrin expression. However, as suggested by the in vitro data, dasatinib seems to decrease integrin activation resulting in decreased binding of [64Cu]DOTA-c(RGDfK).

In conclusion, our study indicates that PET imaging with radiolabeled RGD peptides represents a novel approach for imaging in vivo changes in tumor cell invasiveness in response to dasatinib. In contrast to existing techniques, PET allows longitudinal noninvasive studies that are of great interest for clinical trials, especially in diseases such as glioblastoma where serial biopsies are not feasible.
challenging or impossible for ethical reasons. PET imaging with RGD peptides has already been successfully used clinically to image the αvβ3 integrin in a variety of malignant tumors (10, 11). Therefore, it will be straightforward to test our preclinical findings on monitoring dasatinib therapy with PET in clinical trials. When validated clinically, PET imaging with RGD peptides could become a unique tool for noninvasive studies of the invasive and metastatic potential of αvβ3-expressing tumors in patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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