Pharmacologic Blockade of FAK Autophosphorylation Decreases Human Glioblastoma Tumor Growth and Synergizes with Temozolomide

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Abstract
Malignant gliomas are characterized by aggressive tumor growth with a mean survival of 15 to 18 months and frequently developed resistance to temozolomide. Therefore, strategies that sensitize glioma cells to temozolomide have a high translational impact. We have studied focal adhesion kinase (FAK), a tyrosine kinase and emerging therapeutic target that is known to be highly expressed and activated in glioma. In this report, we tested the FAK autophosphorylation inhibitor, Y15, in DBTRG and U87 glioblastoma cells. Y15 significantly decreased viability and clonogenicity in a dose-dependent manner, increased detachment in a dose- and time-dependent manner, caused apoptosis, and inhibited cell invasion in both cell lines. In addition, Y15 treatment decreased autophosphorylation of FAK in a dose-dependent manner and changed cell morphology by causing cell rounding in DBTRG and U87 cells. Administration of Y15 significantly decreased subcutaneous DBTRG tumor growth with decreased Y397-FAK autophosphorylation, activated caspase-3 and PARP. Y15 was administered in an orthotopic glioma model, leading to an increase in mouse survival. The combination of Y15 with temozolomide was more effective than either agent alone in decreasing viability and activating caspase-8 in DBTRG and U87 cells in vitro. In addition, the combination of Y15 and temozolomide synergistically blocked U87 brain tumor growth in vivo. Thus, pharmacologic blockade of FAK autophosphorylation with the oral administration of a small-molecule inhibitor Y15 has a potential to be an effective therapy approach for glioblastoma either alone or in combination with chemotherapy agents such as temozolomide.

Introduction
Malignant glioblastoma is an infiltrative brain tumor in which improvements in survival have been largely refractory to advances in surgical and radiologic techniques and focused primarily on the use of temozolomide therapy. The unmet clinical need remains in the development of novel therapies that can cross the blood–brain barrier and either directly reduce glioma tumor growth or sensitize gliomas to temozolomide therapy.

Focal adhesion kinase (FAK) is a 125 kDa nonreceptor tyrosine kinase that was shown to be overexpressed in brain tumors (1). As a coordinator of extracellular inputs (i.e., integrins and growth factor receptors) with intracellular signaling pathways (i.e., sequestration of death receptors and prosapoptotic proteins such as p53, neurofibromin and others; refs. 2–5), FAK is well-established mediator of cell survival and invasion.

The functional role of FAK in glioma cells is based on the observation that glioma cells overexpress FAK with an increased level of FAK autophosphorylation (1). Overexpression of FAK in serum-starved glioblastoma cells results in increased cell motility (6), whereas expression of Y397-mutant FAK or downregulation of FAK with FAK siRNA inhibits basal and PDGF-induced cell migration (6). While FAK is a therapeutic target in glioma cells themselves, targeted deletion of FAK in glioma-associated vascular endothelium resulted in a vascular normalization phenotype associated with a reduction in glioblastoma tumor growth (7). The recent development of small-molecule inhibitor targeting ATP-binding site of FAK, TAE226, was developed by Novartis and has been shown to increase glioblastoma apoptosis and inhibit tumor growth (8). However, this inhibitor was not specific due to targeting of the conservative ATP-binding domain, which contained the conservative sequences common to other tyrosine kinases, causing inhibition of multiple pathways.

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Note: Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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doi: 10.1158/1535-7163.MCT-12-0701
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Because FAK has been highly autophosphorylated in glioblastoma, we focused on targeting the FAK autophosphorylation Y397 site with FAK inhibitor Y15 or inhibitor 14, developed in our group and showed specific inhibition of the FAK autophosphorylation site to block tumor growth in non-central nervous system (CNS) models (9–11). Y15 specifically inhibited FAK autophosphorylation without affecting other kinases (9). The advantage of this inhibitor is that it targets the main autophosphorylation site of FAK rather than the more conserved ATP-binding domain. Once the Y397 site becomes phosphorylated, SH2-containing proteins, such as Src and phosphoinositide 3-kinase (PI3K), bind to FAK, leading to downstream signaling, accompanied by functional cellular changes (12).

In this study, we tested the effect of the FAK autophosphorylation inhibitor Y15 alone or in combination with temozolomide in DBTRG, a human glioma-derived cell line (7) and U87 glioblastoma cell lines. This is the first report that showed that inhibition of FAK autophosphorylation in glioblastoma has potential to be an effective approach to inhibit glioblastoma tumor growth that is more effective in combination with temozolomide.

Materials and Methods

Cell lines

The early passages of patient-derived human DBTRG glioblastoma cells were from Dr. Brian Eliceiri (University of California at San Diego, San Diego, CA), described by Kruse and colleagues (13), and purchased from American Type Culture Collection (ATCC). The DBTRG cells were passaged for less than 6 months after resuscitation of frozen aliquots and no other authentication was carried out. The DBTRG cells were maintained in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% FBS. A total of 1 μg/mL streptomycin, 1 μg/mL L-glutamine, 1 μg/mL sodium pyruvate, 1 μg/mL nonessential amino acids, and 500 μL of insulin 10 mg/mL. U87 glioblastoma cell line was purchased from ATCC and authenticated by ATCC in 2009 by short tandem repeat analysis. The U87 cell line was maintained in minimum essential medium with 10% FBS with 1 μg/mL streptomycin. D37 and U251 glioblastoma cell lines were obtained as a gift from Drs. Michael Ciesielski and Robert Fenstermaker (Roswell Park Cancer Center, Buffalo, NY; no authentication was carried by the authors) and maintained in DMEM medium.

Antibodies

Monoclonal anti-FAK antibody, caspase-3, -8, and anti-PARP antibodies were obtained from Millipore, Inc. Polyclonal antiphospho-tyrosine 397-FAK were obtained from Biosource Inc. Monoclonal anti-β-actin antibodies were obtained from Sigma.

Small-molecule inhibitors

The small-molecule inhibitor Y15 (or inhibitor 14), 1,2,4,5-benzenetetraamine tetrahydrochloride was described in ref. (9) and ordered from Sigma Inc. Temozolomide was obtained from Sigma. The control FAK inhibitor, TAE226 (8) was obtained from Novartis Inc. The Y15-5 derivative 3,3′-diaminobenzidine tetrahydrochloride was ordered from Sigma, and obtained from Drs. Manivannan Ethirajdan and Ravindra Pandey (Roswell Park Cancer Institute).

Western blotting

A total of 1 to 2 × 10⁶ cells were plated on 100 mm² plate, and after 24 hours Y15 and temozolomide compounds were added for 24 hours. Western blotting was carried out by the standard procedure (3).

Immunostaining and immunohistochemistry

A total of 10⁵ cells were plated on the 24-well plate glass coverslips, and next day Y15 was added to the cells for 24 hours. The immunostaining was conducted with phospho-Y397 and FAK and then with secondary Alexa-Red antibodies, as described (14). Actin was stained with phallolidin-fluorescein isothiocyanate (FITC) and nuclei were stained with Hoechst. The slides were analyzed under Zeiss Axiovert fluorescent microscope with ×100 objective. Immunohistochemistry staining was conducted on paraffin-embedded tumor samples in the Pathology Core Facility (Roswell Park Cancer Institute), as described (9).

Cell viability

A total of 1 × 10⁴ cells were plated in a 96-well plate. After 24 hours, cells were treated with small-molecule compounds for 24 hours. Dimethyl sulfoxide (DMSO) was added as a negative control. The MTS compound from Promega 96-well Viability kit was used according to the manufacture’s protocol.

Clonogenicity

The 500 to 1,000 cells were plated in 6-well plates. After 24 hours, different doses of Y15, Novartis inhibitor TAE226, and Y15-5 derivative at 10 μmol/L doses were added to the cells, which were incubated with inhibitors at 37°C for 1 to 2 weeks. Then cells were fixed in 25% methanol and stained with Crystal Violet and colonies were counted in 2 independent experiments.

Detachment

The 2 × 10⁵ cells were plated in 6-well plates and treated 24 hours after plating with different concentrations of Y15 and incubated for 24 to 96 hours. The detached and attached cells were collected and counted at different time points under the microscope using a hemacytometer. The percentage of detached cells was calculated by dividing the number of detached cells by the total number of cells in 4 independent experiments.
**Apoptosis**
Detached cells were collected and fixed in 3.7% formaldehyde for the apoptosis assay. Detection of apoptosis was done with Hoechst 33342 staining and by flow-cytometry analysis. The $1 \times 10^6$ cells were treated with Y15 and temozolomide compounds for 48 hours, and apoptosis was also determined using PE Annexin V and 7-aminoactinomycin staining using BD Pharmingen kit according to the manufacturer’s protocol in the Flow Cytometry Facility (Roswell Park Cancer Institute).

**Invasion**
The cell invasion assay was conducted on 24-well plates using Boyden chambers coated with extracellular matrix, ECMatrix using the Chemicon International Inc. Kit according to the manufacturer’s protocol. The $1 \times 10^5$ cells in serum-free medium were plated into Boyden chamber inserts, and complete medium with 10% serum was added to the bottom of the wells. After 24 hours, Y15 was added to the cells for 24 hours, and invaded cells through the chamber pores were stained and processed by colorimetric reading at 560 nm in a 96-well plate on spectrophotometer. The invasion data were normalized to viability MTT data.

**Flow cytometry**
The $1 \times 10^6$ cells were treated with inhibitors for 48 hours and analyzed by flow cytometry for cell-cycle analysis and apoptosis by the standard procedure in the Flow Cytometry Facility (Roswell Park Cancer Institute).

**Tumor growth in xenograft nude mice**
Six-week-old female nude mice were maintained in the animal facility, and all experiments were carried out in compliance with NIH animal use guidelines using Institutional Animal Care and Use Committee (IACUC) protocol approved by the Roswell Park Animal Care Committee. The $2 \times 10^6$ cells were injected into mice subcutaneously. Y15 was introduced by gavage orally at 100 mg/kg dose daily either next day or 6 days after cell injection alone or in combination with temozolomide. Before start of the treatment, mice were randomized into 4 groups ($n = 5$) with an equal average tumor volume equal to 76 mm$^3$. Temozolomide was administered 6.25 mg/kg orally by gavage every day 5 days a week. The control group was treated with 1× PBS. The mice were treated every day 5 days per week for several weeks. Tumor volume in mm$^3$ was determined, as described (9), and at the end of experiment tumor weight was determined in grams. The mice body weight was determined in grams once a week in all tested groups.

**Intracranial stereotactic injections and Y15 treatment**
Immunodeficient Rag2 knockout mice were used for xenograft studies based on previous studies (15, 16). All animal handling procedures were approved by the University of California at San Diego IACUC. After immobi-
conducted detachment assays at 24, 48, 72, and 96 hours in DBTRG and at 24 and 48 hours in U87 cells (Fig. 2A). Y15 significantly increased cell detachment at a 10 μmol/L dose in DBTRG cells, reaching an average detachment of 21% at 48 hours and 35% to 36% at 72 to 96 hours and reaching the maximal detachment of 81% to 82% at 20 μmol/L at 72 and 96 hours (Fig. 2A, top). The same result was obtained at the higher 50 and 100 μmol/L doses, in which detachment significantly increased at 48 hours and reached 70% and 86%, respectively and reached maximum detachment at 50 μmol/L at 72 and 96 hours. In U87 cells, detachment also increased in a dose- and time-dependent manner (Fig. 2A, bottom), reaching maximal level of 96.5% detachment at 10 μmol/L dose at 48 hours. Thus, Y15 effectively caused detachment in DBTRG and U87 cells.
To detect apoptosis, DBTRG and U87 cells were analyzed by Hoechst staining and apoptotic nuclei were detected starting at 10 μmol/L dose and increased at 20 μmol/L dose in DBTRG cells (Fig. 2B, left), reaching more than 90% at higher doses. The apoptotic nuclei were also detected in U87 cells at 10 and 50 μmol/L doses (Fig. 2B, right). Thus, Y15 significantly increased glioblastoma cell detachment in a dose- and time-dependent manner and caused cell apoptosis.

**Y15 decreased DBTRG and U87 glioblastoma cell invasion**

To test if Y15 decreased cell invasion, we treated DBTRG (Fig. 2C, left) and U87 (Fig. 2C, right) cells with different doses of Y15 and conducted an invasion assay using ECMatrix-coated Boyden chambers. To focus only on viable cells, invasion data were normalized to viability data. Y15 significantly decreased cell invasion in both cell lines (Fig. 2C, right and left). Thus, Y15 decreased DBTRG and U87 glioblastoma cell invasion *in vitro*.

**Y15 inhibited FAK autophosphorylation, activated caspase-8, changed cell morphology, and caused cell rounding in DBTRG and U87 glioblastoma cells**

To test the effect of Y15 on FAK autophosphorylation activity in DBTRG and U87 glioma cells, we treated cells with different doses of Y15 and conducted Western blotting with phospho-Y397-FAK antibody (Fig. 3A). Y15 effectively decreased phospho-Y397-FAK in a dose-dependent manner in both cell lines, whereas it did not affect total FAK in DBTRG cells (Fig. 3A, left). Y15 decreased more significantly Y397-FAK than total FAK in U87 cells (Fig. 3A, right). Y15 also decreased uncleaved caspase-8 in DBTRG and in U87 cells starting 10 μmol/L dose (Fig. 3A). Thus, Y15 caused a dose-dependent decrease of FAK autophosphorylation and activated caspase-8 in DBTRG and U87 cells.

To test the effect of Y15 on cell morphology, Y397-FAK and FAK localization, we conducted immunostaining of FAK, Y397-FAK (red), and actin (green) in DBTRG (Fig. 3B, top) and U87 cells (Fig. 3B, bottom), treated with 1 and 10 μmol/L of Y15. Y15 caused decrease of phospho-Y397-FAK and decreased localization of Y397-autophosphorylated (Fig. 3B, top left) and total FAK (Fig. 3B, top right) in focal adhesions, filopodia, and cytoplasm starting with 1 μmol/L of Y15 in DBTRG cells and increased localization of FAK in the perinuclear/nuclear area. The enlarged merged images of Y397-FAK, FAK, and actin staining are shown in Supplementary Fig. S1. In addition, actin staining showed that Y15 changed cell morphology from elongated polarized motile cells to the rounded cells, especially at 10 μmol/L.
The same effects were observed in U87 cells (Fig. 3B). Thus, Y15 decreased Y397-FAK phosphorylation, changed its localization in focal adhesions and cytoplasm, decreased cell polarization, and caused cell rounding.

Y15 decreased glioblastoma tumor growth, inhibited FAK autophosphorylation, activated PARP and caspase-3 in tumor xenografts.

Next, we tested the effect of Y15 on DBTRG glioblastoma tumor growth at 100 mg/kg delivered orally.
over a 64-day period. Y15 significantly ($P < 0.05$) decreased glioblastoma xenograft tumor growth (Fig. 4A, top left). The tumor sizes were significantly less in Y15-treated mice as compared with untreated (PBS-treated) mice (Fig. 4A, top right). Y15 significantly decreased tumor volume (Fig. 4B, left) and tumor

![Graph showing tumor volume over time](image)

Figure 4. A, Y15 decreased glioblastoma tumor growth. A, Y15 decreased tumor growth in DBTRG xenograft model. Top left, $2 \times 10^6$ DBTRG cells were injected into nude mice. Y15 was delivered orally at 100 mg/kg every day 5 d/wk for 64 days. Top right, The Y15 inhibitor significantly decreased the size of Y15-treated tumors. Bottom, Y15 did not decrease mice body weight. B, Y15 significantly decreased tumor volume and tumor weight. C, $P < 0.05$, Y15-treated versus untreated. Student t test. C, Y15 decreases Y397 autophosphorylation and activates PARP cleavage in tumor xenograft tissues by Western blotting. D, Y15 decreases Y397 autophosphorylation and activates caspase-3 in tumor xenograft tissues by immunohistochemical staining.
weight (Fig. 4B, right) without effect on mice body weight (Fig. 4A, bottom).

In addition, Y15 significantly decreased Y397-FAK and PARP in Y15-treated compared with untreated mice by Western blotting in most tumor xenografts (Fig. 4C). Immunohistochemical staining analysis showed significantly decreased Y397-FAK and increase of cleaved caspase-3 in Y15-treated tumor samples (Fig. 4D). Thus, Y15 significantly decreased glioblastoma tumor growth at 100 mg/kg by oral delivery in vivo, which was accompanied by decreased autophosphorylation of FAK and activation of caspase-3 and PARP cleavage in Y15-treated xenograft tumors.

**Y15 prolonged mice survival in orthotopic xenograft glioblastoma model**

We then determined the effect of Y15 on glioblastoma survival using an orthotopic xenograft model. Mice treated with Y15 showed significantly prolonged survival (P = 0.03) in orthotopic xenograft glioblastoma model compared with the control 1 × PBS-treated group (Fig. 5A). In addition, harvested brain tumors stained with hematoxylin and eosin showed reduced tumor size (Fig. 5B). Thus, these results on prolonged mouse survival in orthotopic mouse model confirm the in vivo xenograft studies on reduced tumor growth in Y15-treated mice.

**Combination of Y15 and temozolomide decreased cell viability and activated caspase-8 more significantly than each inhibitor alone in DBTRG and U87 cells**

To test the combination of the standard chemotherapy drug for treatment of glioblastoma with Y15, we treated DBTRG (Fig. 6A, left) and U87 (Fig. 6, right) cells with 100 μmol/L temozolomide (TMZ) and 10 μmol/L Y15 alone and combination of Y15 and temozolomide. The combination of temozolomide and Y15 more significantly decreased viability of DBTRG and U87 glioblastoma cells compared with each inhibitor alone and untreated cells (Fig. 6A). The same effect was observed in U251 and D37 glioblastoma cells (Supplementary Fig. S2). Thus, combination of Y15 and temozolomide more significantly decreased glioblastoma cell viability compared with each drug alone.

To test the effect of combination of Y15 and temozolomide on apoptosis, we treated DBTRG and U87 cells with Y15, temozolomide, and combination of Y15 and temozolomide and conducted Western blotting with Y397-FAK, FAK, and caspase-8 antibodies (Fig. 6). Y15 decreased Y397-FAK in DBTRG and U87 cells, and caspase-8 was activated more in both cell lines, treated with Y15+TMZ than in cells without temozolomide (Fig. 6B). To confirm activation of caspase-8 and find increased apoptosis, we treated U87 cells with a combination of Y15 and temozolomide as well as with each drug alone.
and analyzed cells by flow cytometry (Fig. 6C). The combination of Y15 and temozolomide increased apoptosis to 59% in U87 cells compared with untreated, Y15- and temozolomide-treated cells (Fig. 6C). The significant increase of apoptosis in case of Y15 and temozolomide combination compared with each agent alone was shown by Annexin V staining (Fig. 6D). Thus, combination of Y15 and temozolomide decreased cell viability and increased apoptosis and activated caspase-8 more significantly than each agent alone in DBTRG and U87 cell lines.

**The combination of Y15 and temozolomide blocked tumor growth in U87 xenografts**

Because combination of Y15 and temozolomide caused a significant increase of apoptosis in U87 cells, we tested the effect of combination of Y15 and temozolomide in the U87 xenograft model in vivo (Fig. 6E, top). The treatment with Y15, temozolomide, and combination started at day 6, when the average tumor volume reached 76 mm\(^2\) and was equal in each group of mice (Fig. 6E). The combination of Y15 and temozolomide effectively blocked tumor growth in U87 xenografts.
growth in the U87 xenograft model in contrast to Y15 and temozolomide. At the end of experiment, there were no tumors present in the combination therapy group. The mice body weight was not significantly affected in each treatment group (Fig. 6E, bottom). We stopped the treatment in this group at day 49 and these tumors did not recur in any of the Y15 and temozolomide-treated mice over an additional period of time, for a total 80 days (not shown). Thus, the combination of Y15 with temozolomide synergistically blocks U 87 tumor xenograft growth.

Discussion

This is the first study showing that inhibition of FAK with small-molecule inhibitor Y15 is an effective approach in blocking glioblastoma tumor growth, especially in combination with temozolomide.

In this study, the pharmacologic blockade of FAK was achieved using an allosteric approach that targeted the major autophosphorylation site of FAK at Y397, and not the active ATP-binding site. This approach has the advantage of higher specificity in targeting FAK because it avoids the sites in the kinase domain that are most highly conserved among tyrosine kinases. The Y15 FAK inhibitor that we used is highly specific to FAK and it did not target other kinases, as we have shown (9). Most of the existing FAK inhibitors target the ATP-binding site within the kinase domain and many have shown problems with cross-reactivity with other kinases or other off-target effects. For example, TAE226 targeted not only FAK, but IGFR and other kinases and was highly toxic (18). Another inhibitor, PF-271 has been shown to inhibit not only FAK, but also homologous kinase Pyk-2 (19). A recently developed PND-1186 inhibitor, also targeting the ATP-binding site, effectively inhibited not only FAK, but also FLT-3, ACK-1, and Aurora-A (20, 21). Thus, to effectively target FAK, new small-molecule inhibitors and new approaches to this molecule are needed.

The high invasion of brain tumors is one of the leading causes of patient death and resistance to chemotherapy. FAK has been shown to be both highly autophosphorylated in brain tumors (1), and linked to brain tumor invasion (2). We have shown in vitro that by targeting the autophosphorylation site of FAK in glioblastoma cell lines, we decreased glialoma invasion in vitro. In addition, our recent observations in mice with targeted deletions of FAK in the vascular endothelium suggests that FAK blockade may also enhance the perfusion of chemotherapeutics in brain tumors by increasing vascular normalization (7). Thus, our data showing the efficacy of Y15 in decreasing gliala progression may have additional therapeutic benefit when used in combination with temozolomide. The detailed study of vascular normalization and invasion in glioblastoma in vivo treated with Y15 will be conducted in the future report.

Thus, these data showed that Y15 is an effective inhibitor in decreasing glioma viability and tumor growth. These results suggest that Y15 may be an effective therapeutic inhibitor for treatment of human glioblastoma in combination with temozolomide.

Disclosure of Potential Conflicts of Interest

V.M. Golubovskaya is the co-founder of CureFAktor Pharmaceuticals, LLC and has ownership interest (including patents) in the company. W.G. Cance is the founder and chief scientific officer of CureFAktor Pharmaceuticals, LLC and has ownership interest (including patents) in it. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: V.M. Golubovskaya, W.G. Cance

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Yemma, C.D. Morrison, J. Lee, B.P. Eliceiri

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Huang, J. Lee, B.P. Eliceiri, W.G. Cance

Writing, review, and/or revision of the manuscript: V.M. Golubovskaya, G. Huang, J. Lee, W.G. Cance

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Acknowledgments

The authors thank the Pathology Core Facility at Roswell Park Cancer Institute for immunohistochemical staining. The authors also thank Dr. Paul Wallace and Mr. Craig Jones at Flow Cytometry Core Facility, Roswell Park Cancer Institute for flow cytometry and apoptosis analyses.

Grant Support

The research is supported by Susan Komen for the Cure Foundation grant BCTR0707148 (V.M. Golubovskaya), National Cancer Institute (NCI) RO-1 grants CA65910 (W.G. Cance) and NIH Heart, Lung and Blood Institute RO-1 72396 (B.P. Eliceiri) and partly by the NCI Cancer Center Support grant to the Roswell Park Cancer Institute (CA 16056).

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Received July 12, 2012; revised November 30, 2012; accepted November 30, 2012; published OnlineFirst December 12, 2012.

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