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CXCL12-induced upregulation of FOXM1 expression promotes human glioblastoma cell invasion

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor; it is highly aggressive and is associated with a poor prognosis. Binding of the chemokine CXCL12 to its receptors (CXCR4 and CXCR7) contributes to the activation of many downstream signaling pathways and promotes the invasion of various malignant tumor cells, including GBM cells. FOXM1, a transcription factor involved in cell cycle regulation, is overexpressed in GBM and is involved in GBM progression. However, the molecular mechanisms by which CXCL12 promotes the invasion of human GBM cells remain unclear. In this study, we demonstrate that CXCL12 increases the production of FOXM1 by binding to CXCR4 in GBM cell lines. Furthermore, pretreatment with an inhibitor of the PI3K/AKT pathway abrogated the CXCL12-induced expression of FOXM1. In addition, there was a positive correlation between CXCL12/CXCR4 expression and FOXM1 expression in human malignant glioma tissues. Finally, a functional assay revealed that CXCL12 does not stimulate GBM cell invasion when FOXM1 expression is silenced using a small interfering RNA (siRNA). Collectively, these findings suggest that CXCL12 promotes GBM cell invasion in part by increasing the expression of FOXM1, which is mediated in part by a PI3K/AKT-dependent mechanism in vitro.

1. Introduction

Glioblastoma multiforme (GBM), a World Health Organization (WHO) grade IV astrocytoma, is the most common primary malignant tumor of the central nervous system (CNS) [1]. Despite multimodal treatments, including microsurgical resection followed by radiotherapy and chemotherapy, the prognosis of patients with GBM remains poor; GBM patients have a median survival time of only 15 months [2]. Therefore, new therapeutic approaches for the treatment of GBM are urgently needed.

The chemokine system comprises approximately 50 ligands and 20 receptors in humans, and is involved in many aspects of CNS development and brain tumorigenesis [3,4]. Activation of the CXCL12/CXCR4/CXCR7 chemokine axis has been observed in prostate cancer, breast cancer, lung cancer, ovarian cancer, and brain tumors [5]. An increasing number of studies have focused on the signals downstream of the CXCL12/CXCR4/CXCR7 axis, and explored the contribution of these signals to glioma progression. The CXCL12/CXCR4 axis contributes to the activation of several downstream pathways, including the PI3K/AKT pathway, the ERK1/2 pathway, Ca2+ influx, and the JAK/STAT pathway; the activation of these pathways are correlated with GBM progression as well as resistance to traditional therapies [6–8]. In this study, we sought to further determine the potential downstream mediators of the CXCL12/CXCR4/CXCR7 axis that are involved in GBM progression.

FOXM1, a key cell-cycle regulator of both the G1-S and G2-M transitions, regulates the transcription of cell-cycle genes essential for these phases, including Cdc25A, Cdc25B, cyclin B, cyclin D1, $p21^{cip1}$, and $p27^{kip1}$ [9]. Increasing evidence indicates that the overexpression of FOXM1 is correlated with carcinogenesis and tumor growth in GBM, lung cancer, hepatocellular carcinoma, primary breast cancer, prostate cancer, and pancreatic cancer [10]. Dai et al. reported that FOXM1 promotes glioma cell invasion by

Abbreviations: GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; siRNA, small interfering RNA; CXCL12, chemokine (C-X-C motif) ligand 12; CXCR4, chemokine (C-X-C motif) receptor 4; CXCR7, chemokine (C-X-C motif) receptor7; FOXM1, forkhead box M1.

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directly elevating the expression of MMP2 [11]. PI3K/AKT, ERK1/2, NF-kB, HIF-1, and Gli1 have been reported to regulate FOXM1 signaling [12]. However, the upstream pathway that regulates FOXM1 signaling has not been clearly established in GBM, and requires further investigation.

Aberrant activation of the CXCL12/CXCR4/CXCR7 axis and FOXM1 overexpression have been observed in human GBM. Both of these alterations promote GBM progression. In addition, CXCL12 binding to CXCR4 or CXCR7 contributes to the activation of the PI3K/AKT and ERK1/2 pathways; the activation of these pathways promotes FOXM1 expression. These observations suggest that the CXCL12/CXCR4/CXCR7 axis promotes GBM cell invasion via the upregulation of FOXM1.

2. Materials and methods

2.1. Cell lines and reagents

Human GBM cell lines (A172 and U118MG) were purchased from American Type Culture Collection (Rockville, Maryland, USA). All cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS). Recombinant human CXCL12 was acquired from RD Systems. AMD3100 was acquired from Sigma Aldrich. LY294002 and PD98059 were purchased from Cell Signaling Technology (CST). Anti-CXCL12 and anti-CXCR4 were purchased from Abcam, and anti-CXCR7 were purchased from Gene Tex. Antibodies against AKT, p-AKT, ERK, p-ERK, GAPDH, and FOXM1 were acquired from CST.

2.2. Tissue specimens and immunohistochemical staining (IHC)

In total, 33 GBM and 28 anaplastic astrocytoma (AA) tissue samples were histopathologically diagnosed at the Department of Neurosurgery of Sun Yat-sen Memorial Hospital from 2003 to 2013. The patients provided written informed consent prior to recruitment. The tumor specimens were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned at a thickness of 3 μm. IHC was performed using a two-step IHC kit (Zhong Shan Golden Bridge Biotechnology, China) according to the manufacturer's protocol. The percentage of positive cells and the staining intensity of those cells in each section were analyzed. The total score of each sample was determined by summing the staining intensity results and the percentage of positive cells as previously described [13].

2.3. Small interfering RNA (siRNA) knockdown assay

The siRNAs were synthesized by RIBOBIO Biotechnology (Guangzhou, China) and used to transiently silence the expression of the target genes. Human GBM cells were transfected with 50 nM siRNA using RNAiMAX transfection agent (Life Technologies) according to the manufacturer's instructions. The medium was refreshed 12 h after transfection, and the knockdown assays were performed 48 h after transfection.

2.4. Western blot analysis

Human GBM cells were starved for 24 h and treated as described in the Section 3 after the cells reached 70–80% confluence in 6-well cell culture plates. The cells were lysed in RIPA lysis buffer (CST) supplemented with protease inhibitor and phosphatase inhibitor (Roche). Western blot analysis of equal amounts of total protein was performed as previously described [13]. All experiments were repeated at least three times.

2.5. Quantitative real-time polymerase chain reaction (qRT-PCR)

To assess FOXM1 gene expression, total RNA was extracted from human GBM cells using TRIzol reagent (Life Technologies). cDNA was synthesized using the PrimeScriptTM RT Master Mix Kit (Takara, RR036A), according to the manufacturer's instructions. For the real-time PCR assays, aliquots of double-stranded cDNA were amplified using a SYBR Green PCR Kit (Takara, DDR820A). The cycling parameters were as follows: 95 °C for 30 s, followed by 40 cycles of 95 °C for 5 s and 60 °C for 30 s. The data are presented as the fold change ($2^{-\Delta\Delta Ct}$) relative to the "Control" sample and are representative of three independent experiments.

2.6. Cell invasion assays

A172 and U118MG cells were transfected with siFOXM1 (50 nM) for 12 h and stimulated with CXCL12 (0.1 μg/ml) for 24 h prior to use in invasion assays. Transwell invasion assays were performed using a Transwell system (24-well insert; pore size, 8 μm; Corning Costar) with a polycarbonate filter membrane that was pre-coated with Matrigel, in accordance with the manufacturer's instructions. Homogeneous single-cell suspensions (1.5×10^4 cells/well) in 200 μl of serum-free DMEM were seeded into the upper chambers, and the lower chambers were filled with 600 μl of DMEM containing 10% FBS. After incubation for 12 h, the cells that were attached to lower surface were fixed in methanol for 15 min and stained with 0.1% crystal violet for 10 min. For each membrane, five distinct fields were randomly photographed and counted under a microscope (original magnification, 400×). The data are expressed as the average ± SD of five independent experiments.

2.7. Measurement of CXCL12 protein expression

Cells were plated at a density of 1.5×10^5 cells/well in 6-well plates and maintained in DMEM supplemented with 10% FBS for 24 h. The medium was then changed to serum-free DMEM, and the plates were incubated for an additional 24 h. The level of CXCL12 protein in the culture supernatants was determined using an ELISA kit (RD systems), according to the manufacturer's instructions.

2.8. Statistical analysis

The associations between the expression of FOXM1 and the expression of CXCL12, CXCR4, or CXCR7 were analyzed using Spearman's rank test. Comparisons of quantitative data were analyzed by one-way analysis of variance (ANOVA) to determine significant differences between treatment groups. A P value <0.05 was considered statistically significant. All analyses were performed using SPSS software (IBM SPSS Statistics 19.0).

3. Results

3.1. The expression of CXCL12 and CXCR4 is significantly correlated with FOXM1 expression in human malignant glioma samples

IHC staining of the CXCL12, CXCR4, CXCR7, and FOXM1 proteins was performed on 33 GBM and 28 AA sections. The CXCL12 protein was expressed in the cytoplasm of tumor cells and in endothelial, microglial, and immune cells. High levels of CXCL12 protein were primarily observed in areas adjacent to tumor necrosis (Fig. 1A). FOXM1 protein expression was observed in the nuclei of malignant glioma cells (Fig. 1A). We calculated the correlation between the scores for CXCL12 and FOXM1, which indicated a significant rela-

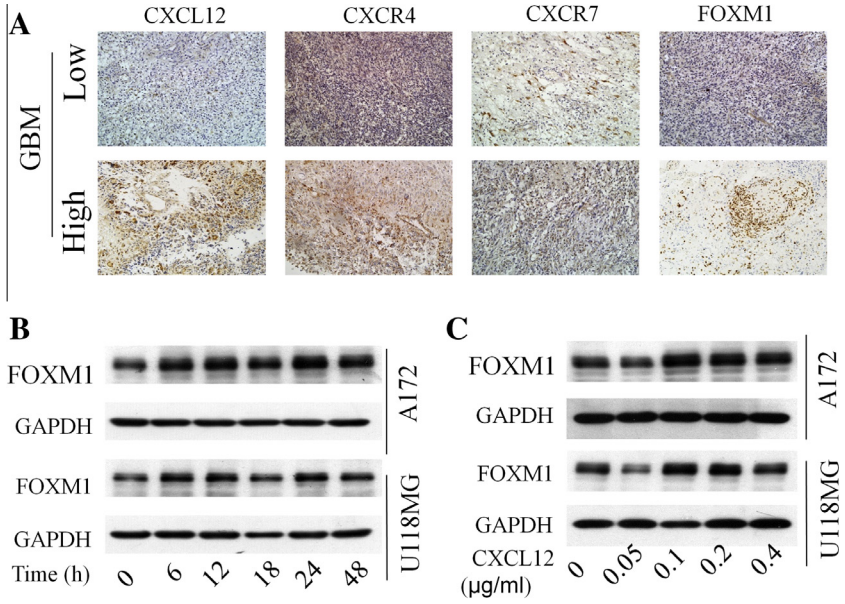

Fig. 1. CXCL12 increases FoxM1 expression in GBM cells. (A) Representative images showing IHC staining (original magnification, 200×) of CXCL12, CXCR4, CXCR7, and FoxM1 expression in human GBM sections. (B) FOXM1 expression was assessed by Western blot after the addition of CXCL12 (0.1 μg/ml) at the indicated time points. (C) A172 and U118MG cells were treated with the indicated concentrations of CXCL12 for 24 h, and the expression of FOXM1 was analyzed. Each result is representative of three independent experiments.

Table 1
FoxM1 expression is positively correlated with CXCL12 and CXCR4 expression, in human GBM and AA tissues.

	GBM		AA	
	r	*P value	*r*	*P value
FOXM1 vs. CXCL12	0.626	<0.0001	0.433	0.0215
FOXM1 vs. CXCR4	0.456	0.008	0.411	0.0298
FOXM1 vs. CXCR7	−0.155	0.391	−0.073	0.7137

* Spearman's rank correlation was used to analyze the relationships between FOXM1 and CXCL12/CXCR4/CXCR7.

tionship (Table 1). We also observed a similar correlation between the expression of FOXM1 and CXCR4, but not between FOXM1 and CXCR7 (Table 1). Therefore, our results suggest that FoxM1 expression is positively correlated with both CXCL12 and CXCR4 expression, in human malignant glioma samples.

3.2. CXCL12 induces FOXM1 expression by binding to CXCR4, but not CXCR7

Because CXCL12 expression was positively correlated with the expression of FoxM1 in human GBM tissues, we assessed the effects of CXCL12 on FOXM1 expression in GBM cell lines. We observed CXCL12, CXCR4, CXCR7, and FOXM1 expression in GBM cell lines (Supplementary Fig. S1A). To study the effect of exogenous CXCL12 on the expression of FOXM1, two GBM cell lines were chosen (A172 and U118MG cells). FOXM1 expression increased in a time- and dose-dependent manner following CXCL12 stimulation; the highest expression was detected at 24 h after the addition of 0.1 μg/ml CXCL12 (Fig. 1B and C). We next transfected GBM cells with CXCL12 siRNA (50 nM) to explore the effect of endogenous CXCL12 on FOXM1 expression. Knockdown of endogenous CXCL12 suppressed FOXM1 expression, and the addition of CXCL12 (0.1 μg/ml) reversed the effect of CXCL12 siRNA (Supplementary Fig. S1B and Fig. 2A). These results demonstrate that both endogenous and exogenous CXCL12 can upregulate FOXM1 expression in GBM cell lines.

We then determined which receptor was involved in the CXCL12-induced upregulation of FOXM1. When AMD3100 (a specific CXCR4 antagonist) was added to GBM cells 1 h before stimulation with CXCL12, the CXCL12-induced expression of FOXM1 mRNA and protein was inhibited (Supplementary Fig. S1C and D, Fig. 2B). In addition, the expression of FOXM1 was suppressed by siRNA knockdown of CXCR4 (Fig. 2C and Supplementary Fig. S2A), but the siRNA knockdown of CXCR7 had no effect on FOXM1 expression (Fig. 2D and Supplementary Fig. S2B). These results indicate that the increase in the expression of FOXM1 was specifically due to the CXCL12/CXCR4 axis. Taken together, these results indicate that CXCL12 enhances FOXM1 expression by binding to the CXCR4 receptor.

3.3. CXCL12 increases FOXM1 expression partially via the PI3K/AKT pathway

The CXCL12/CXCR4 interaction has been reported to contribute to the activation of the PI3K/AKT and ERK1/2 pathways in GBM [14]. We therefore investigated whether these pathways are responsible for the CXCL12-induced expression of FOXM1. First, we analyzed the effects of CXCL12 on the activation of the PI3K/AKT and ERK1/2 pathways in human GBM cell lines (Supplementary Fig. S2C and D). We then investigated the signaling pathway involved in the enhancement of CXCL12-mediated FOXM1 expression in vitro. FOXM1 protein and mRNA expression were markedly antagonized by treatment with the PI3K/AKT inhibitor LY294002 (Fig. 3A, C and D), whereas the ERK1/2 inhibitor PD98059 had no inhibitory effect on FOXM1 expression (Fig. 3B, Supplementary Fig. S3A and B). These results suggest that a PI3K/AKT pathway-dependent mechanism partially mediates the positive regulation of FOXM1 expression by CXCL12 in GBM cell lines.

3.4. CXCL12 promotes human GBM cell invasion in part through FOXM1

Because CXCL12 increases the expression of FOXM1, we next performed Transwell invasion assays to determine if FOXM1 af-

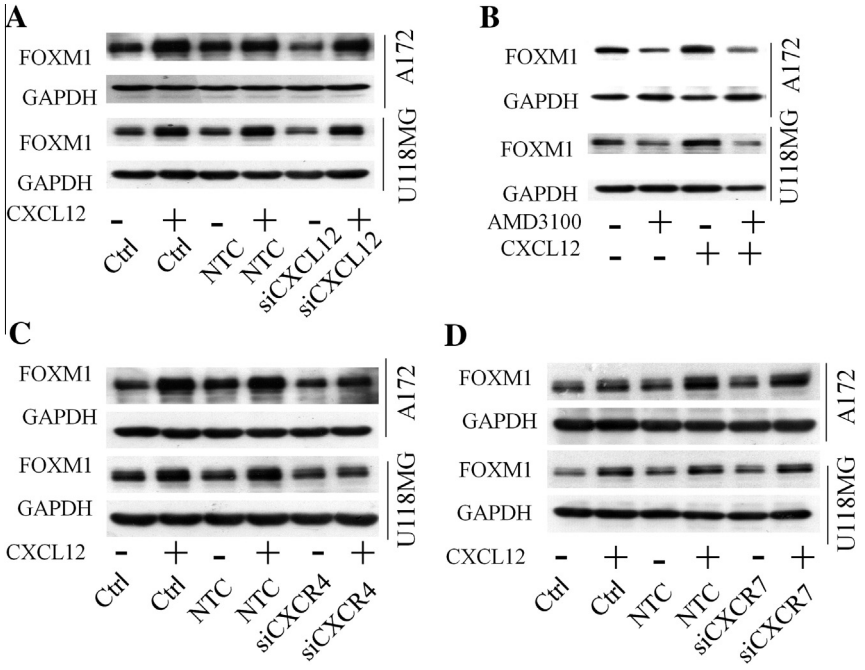

Fig. 2. CXCL12 increases FOXM1 expression by binding to CXCR4, but not CXCR7. (A) CXCL12 siRNA-mediated depletion of endogenous CXCL12 inhibited FOXM1 expression, and the addition of exogenous CXCL12 (0.1 μg/ml) reversed this response. (B) CXCL12-induced FOXM1 expression was suppressed by the CXCR4-specific antagonist AMD3100. (C) The targeted knockdown of CXCR4 abrogated the CXCL12-induced expression of FOXM1. (D) The targeted knockdown of CXCR7 had no effect on CXCL12-induced FOXM1 expression. Each result is representative of three independent experiments. NTC: non-targeted control.

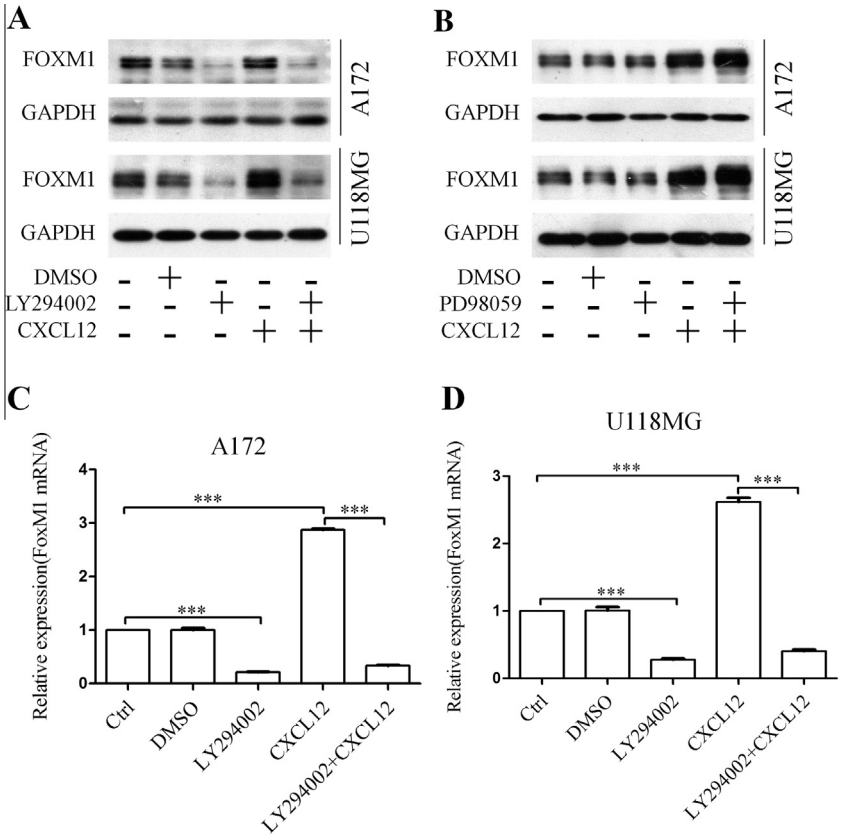

Fig. 3. The CXCL12/CXCR4 axis increases FOXM1 expression partially through activation of the PI3K/AKT pathway. (A and B) The indicated cells were pretreated with LY294002 (20 μM) or PD98059 (20 μM) for 30 min and then incubated with or without CXCL12 (0.1 μg/ml) for an additional 24 h. Western blotting was used to determine FOXM1 protein expression. (C and D) The cells were treated as in "A". qRT-PCR was used to determine FOXM1 mRNA expression. Each result is representative of three independent experiments. DMSO was used as a control. $^{***}P < 0.0001$. ns: no significant difference.

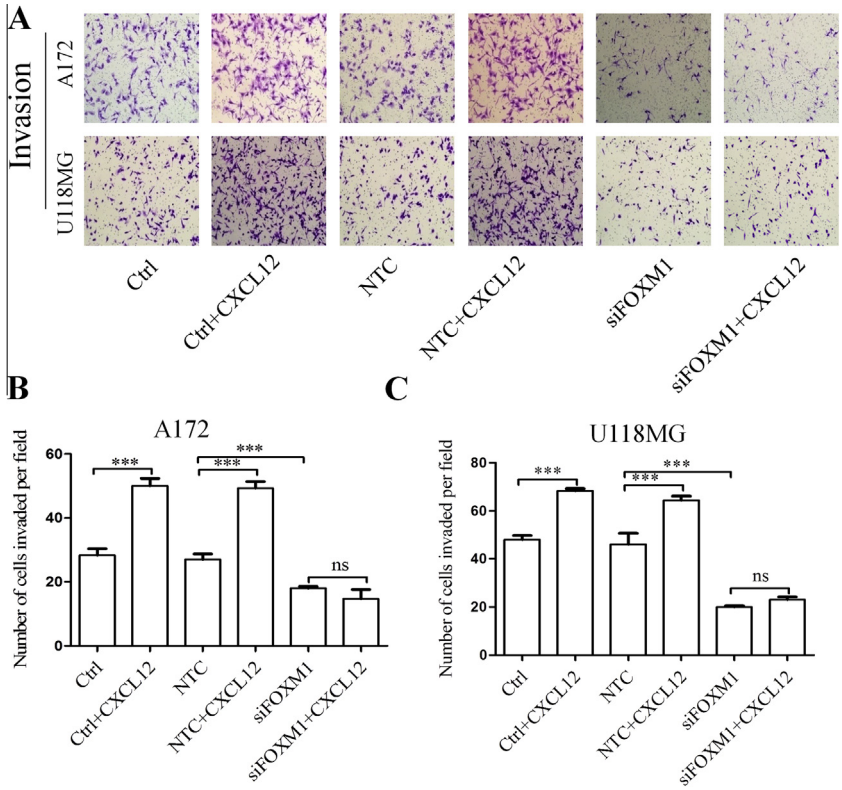

Fig. 4. CXCL12 promotes GBM cell invasion in part via FOXM1. A172 and U118MG cells were subjected to siRNA-mediated knockdown of FOXM1 and/or stimulated with CXCL12 (0.1 μg/ml). CXCL12 had no effect on the invasion of GBM cells when endogenous FOXM1 expression was attenuated by siRNA. (A) Transwell Matrigel invasion chambers were used to assess the invasive of GBM cells subjected to different treatments. The images are shown at the original magnification of 100×. (B and C) For each membrane, five distinct fields were randomly chosen, and the adherent cells were counted under a microscope (original magnification, 400×). The results are shown as the mean ± SD and represent five independent experiments. NTC: non-targeted control. ***$P < 0.0001$. ns: no significant difference.

fects the CXCL12-stimulated invasion of human GBM cells. A specific siRNA was used to transiently silence FOXM1 expression in GBM cells (Supplementary Fig. S3C). CXCL12 significantly increased cell invasion compared to un-stimulated controls (Fig. 4A–C). Knockdown of FOXM1 led to a significant decrease in the cell invasion activity of GBM cells (Fig. 4A–C). Strikingly, CXCL12 did not enhance the invasion activity of GBM cells in which FOXM1 expression was attenuated by siRNA (Fig. 4A–C). Taken together, these findings demonstrate that FOXM1 is critical for the CXCL12-mediated invasion of human GBM cells.

4. Discussion

The CXCL12/CXCR4 signaling axis and FOXM1 play an important role in tumorigenesis and tumor progression in various solid tumors, including GBM [15–17]. In the present study, we demonstrated that the CXCL12/CXCR4 signaling pathway-mediated elevation of FOXM1 expression enhances GBM cell invasion in vitro.

Overexpression of CXCL12 and its receptors, CXCR4 and CXCR7, has been reported in human GBM [18–20]. Zhang et al. determined that FOXM1 is expressed in various regions of human malignant glioma specimens, particularly in tumor cells surrounding necrotic areas [21]. Consistent with previous reports [22], we demonstrated that CXCL12 and CXCR4 are expressed in tumor, endothelial, microglial, and some immune cells. The expression of CXCL12 and CXCR4 was localized mainly in necrotic regions of human malignant glioma specimens; FOXM1 was also overexpressed in these areas. Notably, we demonstrated that the expression of FOXM1 was significantly correlated with CXCL12 and CXCR4 expression in human GBM. We therefore explored the molecular mechanisms by which the CXCL12/CXCR4 axis is linked to the transcription factor FOXM1 in human GBM cells.

CXCL12 is secreted by GBM cells and other cells in the tumor microenvironment, including endothelial cells, neurons, microglia, macrophages, T lymphocytes, and reactive astrocytes surrounding the tumor regions [14]. The CXCL12/CXCR4 complex modulates many downstream effectors in gliomas, such as VEGF, MT2-MMP, and PAI-1 [23–25]. Our data showed that only CXCR4 mediated the CXCL12-induced upregulation of FOXM1 in GBM cell lines. Autocrine or/and paracrine secretion of CXCL12 contributed to promote the expression of FOXM1 through CXCR4. However, the lack of apparent involvement by the CXCL12/CXCR7 axis in this response requires further investigation.

The CXCL12/CXCR4 axis has been implicated in the activation of several signaling effectors, including PI3K/GSK-3β, PI3K/AKT/NF-kB, ERK1/2, and PLCγ/Ca2+, leading to proliferation, survival, angiogenesis, and additional effects in malignant tumors [26]. PI3K/AKT is constitutively activated in GBM, and AKT overexpression is observed in up to 80% of GBMs [27]. Previous studies have shown that ERK/CREB, ROS, HIF-1, PI3K/AKT, and TNF-α regulate FOXM1 expression [10]. However, the molecular mechanisms through which this chemokine axis regulates FoxM1 expression in GBM cells remain largely unknown. In the current study, we determined that CXCL12/CXCR4 promotes FOXM1 expression in part through the activation of the PI3K/AKT pathway. The ERK1/2 signaling pathway was not involved in this response, although this pathway regulates FOXM1 expression in other cancer cells [13]. However, this study did not completely rule out the presence of additional pathways that may contribute to the regulation of FOXM1 expression, which will be addressed in future studies.

CXCL12 promotes GBM cell invasion [23,28], but the detailed mechanisms remain unclear. Here, we demonstrated that the CXCL12/CXCR4 axis promotes FOXM1 expression in GBM cells. Consequently, we speculated that CXCL12 enhances GBM cell invasion via FOXM1. We observed that the addition of CXCL12 (0.1 μg/ml) did not promote GBM cell invasion when FOXM1 expression was abrogated by siFOXM1. Therefore, we suggest that FOXM1 plays an important part in the promotion of GBM cell invasion by CXCL12. We assume that CXCL12 contributes to the invasive behavior, proliferation, and angiogenesis of GBM; investigations are ongoing in our laboratory to further define these effects.

There are some limitations to our study. First, it is unclear if CXCL12 induces the expression of FOXM1 via the PI3K/AKT pathway in other cancer cells. Second, whether the transcription factor FOXM1 can regulate CXCL12 and CXCR4 expression, and establish a positive feedback loop remains unknown. Finally, we did not reproduce these results in vivo. Additional studies are urgently needed to address these questions.

In summary, we demonstrated for the first time that the CXCL12/CXCR4 axis induces the expression of FOXM1 in part through the activation of the PI3K/AKT pathway. Increasing the expression of FOXM1 promotes the invasion of GBM cells. This study provides insight into a novel molecular mechanism of CXCL12-mediated human GBM cell invasion and identifies potential targets for future GBM treatment.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.12.079.

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