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The Role of Chemoattractant Receptors in the Progression of Glioma

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1. Introduction

Chemoattractant receptors are a superfamily of G-protein coupled seven transmembrane cell surface receptors (GPCRs), which transduce extracellular signals into intracellular effector pathways through the activation of heterotrimeric G proteins. This superfamily includes GPCRs for classical chemoattractants such as formyl peptides (fMLF) produced by Gram negative bacteria and host cell mitochondria, the complement cleavage components, leukotriene B₄ (LTB₄), and platelet activating factor (PAF) as well as GPCRs for chemokines (Le et al., 2002).

Chemoattractant GPCRs have the ability to mediate directional migration of cells along a gradient of a chemoattractant. Initially, these receptors were identified mainly on leukocytes, where they play an important role in the trafficking of such cells to sites of inflammation and to lymphoid organs in immune responses (Le et al., 2004). However, during the past few years, both hematopoietic and nonhematopoietic cells have been found to express various chemoattractant GPCRs and are capable of migrating in response to agonists produced in tissue microenvironment. The interaction of chemoattractant GPCRs with their agonists participates in a variety of essential pathophysiological processes including immune responses, inflammation, host defense against microbial infection, hematopoiesis as well as cancer progression and metastasis (Huang et al., 2008).

Chemoattractants and their GPCRs are widely expressed in the brain by neurons, glial and microglia cells. They are involved not only in cell migration during development and inflammation, but also act as regulators of neuronal survival, neurotransmission and cell-cell communications (Ambrosini and Aloiso, 2004), as the third major transmitter system in the brain (Adler and Rogers, 2005). In addition, chemoattractants and their GPCRs are dysregulated in neurodegenerative diseases, multiple sclerosis and brain tumors (Balkwill, 2004; Ransohoff et al., 2007). A number of chemoattractant GPCRs have been detected in glioma cells including FPR1 and chemokine GPCRs (Table 1).

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Chemoattractant GPCRs (expressing cells)	Ligand (cell sources)	Major effects on glioma	References
FPR1 (glioma cells)	fMLF (bacteria); Annexin1 (necrotic glioma cells)	Growth; Invasion; Angiogenesis	Zhou et al., 2005; Huang et al., 2007, 2008, and 2010
CXCR1 (glioma cells)	CXCL8 (glioma cells)	Invasion	Raychaudhuri et al., 2011
CXCR2 (glioma cells)	CXCL8 (glioma cells)	Angiogenesis	Brat DJ et al., 2005
CXCR3 (glioma cells)	CXCL10 (glioma cells) ; CXCL9 (glioma cells)	Proliferation; Growth	Liu et al., 2010; Maru et al., 2008
CXCR4 (glioma cells)	CXCL12 (glioma cells and stromal cells)	Growth; Angiogenesis; Migration	Ping et al., 2007 and 2011
CXCR5 (glioma cells)	CXCL13 (glioma cells)	Not clear	Bajetto et al., 2006
CXCR7 (glioma cells)	CXCL12 (glioma cells and stromal cells)	Anti-apoptosis	Hattermann et al., 2010
CCR2A (glioma cells)	CCL2 (glioma cells)	Migration	Liang Y et al., 2008
CCR3 (glioma cells)	CCL3L1 (glioma cells)	Proliferation	Kouno et al., 2004
CCR4 (Treg cells)	CCL22 (glioma cells)	Treg infiltration	Jacobs et al., 2010
CCR5 (glioma cells)	CCL3L1 (glioma cells)	Proliferation	Kouno et al., 2004
CX3CR1 (glioma cells and GIMs)	CX3CL1 (glioma cells)	Tumorigenesis; Pro-or anti-invasion based on whether CX3CL1 is soluble or membrane bound.	Liu et al., 2008

GIMs: glioma infiltrating macrophages; Treg: regulatory T cells.

Table 1. The expression of chemoattractant GPCRs in glioma

Glioma is the most common tumor type in human brain. Nearly two-thirds of human gliomas are highly malignant with rapid progression, high invasiveness, vigorous angiogenesis and resistance to chemotherapy and radiation treatment (Bar, 2011). Glioblastoma (GBM), the most aggressive form of malignant glioma, is characterized by extensive infiltration into the surrounding normal brain tissues and multifocal necrosis. Despite multiple therapeutic regimens (Jahraus and Friedman, 2010), the 2-year survival rate of patients with GBM is less than 30% and has not changed over the past two decades. Because of the increasing incidence of GBM and very poor prognosis, a better understanding of GBM initiation and progression is crucial for the development of more effective therapeutic approaches. GBM cells utilize the normal physiological functions of chemoattractant GPCRs to promote their growth by sensing cognate ligands produced in the microenvironment that enhance tumor cell proliferation, invasion and the production of angiogenic factors such as vascular endothelial cell growth factor (VEGF) and the chemokine CXCL8 (IL-8) (Yao et al., 2008; Ping et al., 2007). Recently, the chemoattractant GPCRs FPR1 and CXCR4 were also found to be expressed by glioma stem-like cells (GSLCs) and to mediate GSLC chemotaxis and the production of VEGF (Ping et al., 2007; Yao et al.,

2008; Ping et al., 2011), suggesting the important role of these GPCRs in glioma initiation. In this article, we will review the contribution of chemoattractant GPCRs in glioma progression and discuss the potential for GPCRs as therapeutic targets in glioma.

2. The role of the classical chemoattractant GPCR, FPR1, in the progression of GBM

2.1 Identification of FPR1 in GBM

Human FPR1 (originally named FPR) was detected in 1976 on the surface of human neutrophils, and was cloned in 1990 from a myeloid leukemia-cell line. FPR1 binds N-formyl-methionyl-leucyl-phenylalanine (fMLF), a product of the Gram negative bacteria, as well as mitochondria formylated peptide, and elicits a cascade of signal transduction events mediated by pertussis toxin-sensitive G proteins of the Gi subtype and controlled by phospholipase C (PLC) and phosphoinositide (PI) 3 kinases (Pan et al., 2000). Human myeloid cells activated by FPR1 agonist peptides undergo rapid shape change, showing increased adhesion, chemotaxis, phagocytosis and release of bactericidal and proinflammatory mediators. These functions of FPR1 enable myeloid cells to have proinflammatory and antimicrobial activities. In fact, depletion of the human FPR1 counterpart mFPR1 from mice decreased their resistance to infection by *Listeria monocytogenes*. Although FPR1 has been shown to be a GPCR that mediates host defense against bacterial infection by phagocytic leukocytes, we found that FPR1 was also selectively expressed by tumor cells in more highly malignant human glioma specimens (Zhou et al., 2005). These findings prompted us to use established human glioma cell lines to investigate the relationship between FPR1 expression and the biological behavior of the tumor cells. For example, the human GBM cell line U87 expresses higher levels of FPR1 and forms more rapidly growing tumors in nude mice than glioma cell lines derived from low grade gliomas, which do not express FPR1 (Zhou et al., 2005). Therefore, observations with glioma cell lines lead us to hypothesize that FPR1 is selectively expressed by more highly malignant glioma cells and may play a role in promoting tumor growth.

2.2 Function of FPR1 in GBM cells

The function of FPR1 in GBM cells was extensively examined by using the prototype chemotactic agonist peptide, bacterial fMLF as a stimulator. In addition to inducing robust chemotaxis and calcium mobilization of GBM cells by fMLF, FPR1 exhibited several unique properties that are closely related to tumor progression. For instance, activation of FPR1 in GBM cells under suboptimal culture conditions (i.e. at low fetal calf serum (FCS) concentration) supports the survival of tumor cells in association with increased intracellular levels of the anti-apoptotic protein Bcl-2. In addition, FPR1 agonist peptide activated two important transcription factors, namely NF- κ B and STAT3 in GBM cells. Increased NF- κ B translocation has been observed as a consequence of FPR1 signaling pathway also in phagocytic leukocytes (Huang et al., 2001); FPR1 signaling in GBM cells stimulated the phosphorylation of STAT3 at Ser-727 and Tyr-105 residues, while only Ser-727 was phosphorylated in human monocytes. Another transcription factor hypoxia inducible factor-1 α (HIF-1 α), which induces the adaptation to hypoxic microenvironment by regulating the gene transcription in several processes such as cell oxygen uptake, glucose metabolism, angiogenesis, cell survival and apoptosis, was also activated by FPR1 agonists in GBM cells (Zhou et al., 2005).

Since both STAT3 and HIF-1 α are implicated in the transcriptional activation of the gene coding for VEGF, we investigated the effect of activating FPR1 on the production of VEGF by tumor cells. We found that supernatants from fMLF-stimulated GBM cells induced the migration and tubule formation of human vascular endothelial cells (EC) (Zhou et al., 2005). This property of the tumor cell supernatant was abolished by a neutralizing anti-human VEGF antibody (Zhou et al., 2005), suggesting VEGF was released by FPR1 agonist-stimulated GBM cells. FPR1 in GBM cells was subsequently shown to promote the release of another angiogenic factor, the chemokine CXCL8 (IL-8) (Yao et al., 2008). The contribution of FPR1 to GBM progression was then tested *in vivo* in nude mice. Tumor cells containing small interference (si) RNA targeting FPR1 mRNA yielded tumors in nude mice with markedly reduced rate of growth as compared to control cells transfected with random siRNA (Zhou et al., 2005). Thus, the functional studies provide strong evidence for the involvement of FPR1 in supporting the rapid progression of GBM.

Crosstalk between GPCRs and growth factor receptors plays an important role in orchestrating the interaction of intracellular signaling molecules implicated in tumor growth, angiogenesis and metastasis (Lappano and Maggiolini, 2011). The crosstalk between GPCRs and the receptor for epidermal growth factor (EGFR) has been shown to promote the progression of colon, lung, breast, ovarian, prostate, and head and neck carcinomas (Hart et al., 2005). Like many malignant tumors of human and mouse origin, human GBM cells express high levels of EGFR and stimulation with EGF increases tumor cell chemotaxis and proliferation with rapid phosphorylation of at least 4 tyrosine residues in the C-terminal domain of EGFR (Huang et al., 2007). When GBM cells were stimulated with the FPR1 agonist fMLF, EGFR was also rapidly phosphorylated but with restriction to a single tyrosine residue Tyr992. This transactivation of EGFR by FPR1 agonist peptide accounted for approximately 40% of the biological activity of FPR1 in GBM cells and was dependent on a Src kinase pathway (Huang et al., 2007). Moreover, GBM cells depleted of either FPR1 or EGFR grew more slowly as compared with parental cells and depletion of both receptors further reduced the tumorigenicity of the GBM cells (Huang et al., 2007). Thus, FPR1 aberrantly expressed in GBM cells is capable of exploiting the function of EGFR to exacerbate the malignant behavior of the tumor cells. Since interference with both receptors additionally reduced tumor growth, FPR1 and EGFR also had non-redundant functions (Huang et al., 2008).

2.3 The involvement of FPR1 in GBM cell invasion

The ability of GBM cells to invade into surrounding brain tissue is a critical pathological event in the progression of GBM. In the human GBM cell line U87, there are FPR1⁺ and FPR1⁻ subpopulations which could be isolated and cloned. FPR1⁺ cells showed a more “motile” phenotype *in vitro* as compared with cells lacking FPR1 expression (Huang et al., 2010). Moreover, although both FPR1⁺ and FPR1⁻ GBM cells implanted subcutaneously into nude mice developed tumors, only tumors formed by FPR1⁺ cells invaded the surrounding connective tissues. In addition, FPR1⁻ cells transfected with FPR1 showed enhanced mobility *in vitro* and the *in vivo* capacity to form more rapidly growing and invasive tumors in mice. Tumor invasion depends not only on tumor cell mobility, but also on the capacity of tumor cells to secrete metal matrimetalloproteases (MMPs) that degrade extracellular matrix (ECM) and facilitate the detachment of highly motile tumor cells. Stimulation of GBM cells with FPR1 agonist peptide up-regulates the expression of MMP2 and MMP9 and increases the release of pro-MMP2. As reported in the literature, regulation of MMPs is controlled by AP1 transcription factor complex through MAP kinase pathways

and PKC, which are activated by FPR1 agonist in GBM cells. Thus stimulation of FPR1 activates MMPs in GBM cells and increases proteolytic processes in the tumor microenvironment (Huang et al., 2010).

2.4 Identification of endogenous FPR1 agonist released by necrotic GBM cells

Despite extensive characterization of FPR1 function in GBM cells, whether host-derived agonists are present in the tumor microenvironment remains unknown. We tested GBM cell responses to the neutrophil granule protein cathepsin G, which is an endogenous agonist for FPR1 and induces the migration of myeloid cells. We determined that cathepsin G is capable of inducing the migration of GBM cells expressing FPR1 (Sun et al., 2004). However, cathepsin G is unlikely to be present in brain unless substantial tissue damage compromises the blood brain barrier and results in the release of this FPR1 agonist into the brain by neutrophils. We therefore examined other possible sources of potential FPR1 agonists that may act on GBM cells. Since mitochondrial peptides are also potential endogenous FPR1 agonists and GBMs frequently contain necrotic foci in the rapidly growing tumor mass that may release mitochondrial components, we examined the presence of FPR1 agonists in supernatants of necrotic tumor cells. Indeed, supernatants of necrotic GBM cells and tumors formed by GBM cells in nude mice induced potent chemotaxis of live GBM cells as well as a rat basophil leukemia-cell line transfected to express human FPR1 (ETFR cells). The chemotactic activity released by necrotic GBM cells and tumor tissues was blocked by an anti-FPR1 antibody and by a FPR-specific antagonist tBoc-MLF (Zhou et al., 2005). The robust intracellular Ca^{2+} mobilization induced in GBM cells by necrotic GBM cell supernatant attenuated the subsequent cell response to fMLF, suggesting that agonist contained in the supernatants of necrotic tumor cells share a receptor with fMLF (Zhou et al., 2005). Further evidence to support the release of FPR1 agonists by necrotic GBM cells was provided by the observation that the tumor cell supernatant down-regulated FPR1 expressed on the surface of human monocytes and FPR1 expressing ETFR cells. These observations confirm that FPR1 expressed on GBM cells is able to recognize agonist activity released in the tumor microenvironment in a paracrine and/or autocrine loop (Zhou et al., 2005). Our recent effort to characterize the biochemical nature of the FPR1 agonist activity released by necrotic GBM cells revealed that the glucocorticoid binding protein annexin1 (AnxA1), which has been reported to be an agonist for FPR1 and its variant receptor FPR2, can promote tumor cell invasion and angiogenesis. AnxA1 accounts for the majority of the FPR1 agonist activity released by necrotic GBM cells because depletion of AnxA1 from the necrotic tumor supernatant markedly reduced its capacity to stimulate FPR1 on viable GBM cells (Yang et al., unpublished observation). We therefore established a paradigm for the role of FPR1 in GBM progression in which FPR1 in GBM cells by responding to necrotic tumor cell-released agonist such as AnxA1 transactivates EGFR and the two receptors cooperate to promote the growth, invasion, angiogenesis and progression of GBM (Fig 1A).

3. The role of the chemokine GPCR CXCR4 in glioma progression

3.1 CXCR4 and its ligand CXCL12

CXCR4 selectively binds the CXC chemokine stromal cell-derived factor 1 (SDF-1), also known as CXCL12 (Furusato et al., 2010). CXCR4 is normally expressed in a wide variety of cells and tissues. The CXCR4 agonist CXCL12 was first cloned from a murine bone marrow stromal cell line, and was produced in high quantity by marrow stromal cells. In addition to

mediating cell chemotaxis in response to CXCL12, CXCR4 also acts as a co-receptor for CD4 cell entry of T tropic HIV. In mouse models, deletion of CXCL12 or CXCR4 results in embryonic death with defects in the development of cardiac and central nervous systems as well as reduction in hematopoietic stem-cell homing (Zou et al., 1998). CXCR4 is up-regulated in more than 20 different types of malignant tumors (Kryczek et al., 2007). Further studies show that CXCR4 regulates tumor progression by mediating tumor cell proliferation and metastasis as well as angiogenesis.

3.2 The effect of CXCR4 on glioma invasion and metastasis

CXCR4 expression was detected in primary human glioma specimens and the level of CXCR4 was correlated with the degree of malignancy of the tumors. In vitro, CXCR4+ malignant glioma cells secrete its ligand CXCL12, suggesting that two molecules may exert paracrine and autocrine regulation of glioma progression (Bajetto et al., 2006). Studies performed in human GBM specimens demonstrated that tumor cells infiltrating into surrounding brain tissues express higher levels of CXCR4, suggesting CXCR4 expression may define more highly invasive tumor cells. This is corroborated by in vitro experiments showing that invasive human glioma cells overexpress CXCR4 as compared with noninvasive tumor cells (Ehtesham et al., 2006). Invasive cells isolated from rat C6 glioma cell line express both CXCR4 and CXCL12 at high levels (Ehtesham et al., 2006). Moreover, application of CXCR4 antagonist or siRNA targeting CXCR4 in vivo inhibited the invasion of tumors formed by invasive C6 glioma cells.

The invasion process of GBM requires the detachment of invading cells from tumor mass, attachment of tumor cells to ECM components, ECM degradation, and subsequent cell infiltration into surrounding brain tissues. Attachment of tumor cells to ECM components is an essential phase of invasion mediated by integrins that are overexpressed on both glioma cells and tumor vasculature. Recognition of CXCL12 by CXCR4 activates tumor-associated integrins, such as $\alpha 2$, $\alpha 4$, $\alpha 5$, and $\beta 1$ to promote tumor dissemination (Hartman et al., 2004, and 2005). Inhibition of integrin function disrupts GBM cell migration. In vitro, interference of CXCR4 with the urokinase-receptor (uPAR) reduces the adhesion of CXCL12-mediated CXCR4+ GBM cells to collagen, the main component of ECM (Montuori et al., 2010).

ECM degradation by MMPs enhances tumor invasion. In vitro, glioma cells with lower production of MMP-9 show diminished migration and invasion and such cells no longer form tumors following intracranial injection into nude mice. MMP-2 and -9 have been identified as MMPs in high grade gliomas and their level of expression directly correlates with the grade of glioma malignancy (Stojic et al., 2008). Similar to FPR1, CXCR4 mediated glioma invasion in vivo was also associated with its capacity to activate MMPs (Kryczek et al., 2007). It has been reported that CXCR4/ERK/NF- κ B signaling pathway induces the up-regulation of MMPs in glioma cells. Activation of CXCR4 by its ligand CXCL12 also promotes tumor invasion by release of MMP-9.

3.3 CXCR4 in glioma growth and angiogenesis

3.3.1 Role of CXCR4/CXCL12 in malignant glioma growth and survival

The CXCR4 ligand CXCL12 produced by tumor and stromal cells interacting with CXCR4 on tumor cells results in the activation of several downstream pathways, including MAPK/ERK1/2, PI3k and Akt, as well as NF- κ B. These pathways are known to participate in the regulation of cell proliferation and survival in normal or malignant glial cells. In vitro

activation of CXCR4 promotes the proliferation of GBM cell lines based on the activation of ERK1/2 and PI3K/Akt (Bian et al., 2007). In agreement with data obtained from GBM cell lines, 80% of clinical GBM samples express high levels of phosphorylated Akt (Hambardzumyan et al., 2008). CXCL12 induces the proliferation of primary GBM cells expressing CXCR4 by significantly increasing DNA synthesis in tumor cells (do Carmo et al., 2010). CXCR4-mediated tumor cell proliferation may also be amplified by EGFR signaling, since stimulation of CXCR4 has been reported to transactivate EGFR in many tumors of the epithelial lineage (Dolce et al., 2011). In fact, as discussed earlier, EGFR in GBM cells is transactivated by another chemoattractant GPCR FPR1, and the two receptors co-operate to promote the growth of GBM (Huang et al., 2007). The role of CXCR4 in promoting glioma growth was further supported by the use of a small molecule CXCR4 antagonist, AMD3100, which significantly inhibited tumor cell proliferation in vitro and tumorigenicity in nude mice (do Carmo et al., 2010; and Dolce et al., 2011).

Another important property of CXCR4 is to increase GBM cell resistance to apoptosis. Blockade of CXCR4 in glioma cells by the antagonist AMD3100 increased the rate of apoptosis, confirming the ability of CXCR4 to support tumor cell survival (do Carmo et al., 2010). This anti-apoptotic effect is associated with the activation of PI3K/Akt (do Carmo et al., 2010), an observation consistent with results obtained from a variety of tumors in which CXCR4 actively contributes to the resistance of tumor cells to apoptosis. Stimulation of CXCR4 activates NF- κ B, which in turn inhibits radiation-induced TNF- α production by glioma cells and increases tumor cell survival. In addition to directly protecting tumor cells from radiation-induced apoptosis, CXCR4 indirectly promotes cell survival by increasing their adherence. For example, stimulation of CXCR4 promotes the adhesion of glioma cells to vitronectin, a glioma-derived extracellular matrix protein, and prevents tumor cell death (do Carmo et al., 2010). Taken together, published results support the conclusion that CXCR4 plays an important role in promoting the proliferation and survival of glioma cells.

3.3.2 CXCR4 promotes the production of angiogenic factors by glioma cells

The requirement of CXCR4 and CXCL12 for angiogenesis was revealed by the prenatal lethal phenotype of both CXCR4 and CXCL12 knockout mice due to defects in the vascular development of gastrointestinal tract and cardiogenesis (Tachibana et al., 1998). In vitro, activation of CXCR4 in ECs stimulates the formation of capillary-like tubules (Salvatore et al., 2010). ECs in gliomas have been shown to be genetically and functionally distinct from normal ECs, and exhibit higher expression of CXCR4 and its ligand CXCL12. Proliferating ECs in GBM are positive for CXCR4 and its ligand CXCL12, while ECs that form a single layer in the capillaries of the anaplastic astrocytoma appeared to be negative for these two molecules. The lower levels of CXCR4/CXCL12 expression in anaplastic astrocytoma may contribute to the lower density of proliferating microvasculature. Consistent with these observations, CXCR4 and CXCL12 are detected in both malignant glioma cells and vascular ECs are associated with increased cell survival (Salmaggi et al., 2004).

Interestingly, elevated CXCL12 levels by themselves in gliomas failed to induce significant vascularization. This was associated with the co-presence of low levels of VEGF, suggesting synergism of these angiogenic factors (Kryczek et al., 2005). In fact, although a major angiogenic factor in GBM, VEGF was detected only in a few cells or not at all in low-grade astrocytomas or in the normal brain tissue (Takano et al., 2010). Clinical and experimental evidence indicates that CXCR4 activation induces the production of VEGF in human glioma

cells and glioma stem-like cells (Ping et al., 2007 and 2011). Therefore, CXCR4 may contribute to the production of VEGF by malignant glioma cells and the two pro-angiogenic factors synergistically promote angiogenesis in tumor. In addition to VEGF, the activation of CXCR4 in gliomas also is associated with increases the secretion of an angiogenic chemokine, CXCL8 (IL-8) (Ping et al., 2007). Interestingly, VEGF binds the receptors on ECs and leads to the up-regulation of the anti-apoptotic molecule Bcl-2 as well as the release of CXCL8 from ECs (Nör et al., 2001). CXCL8 then is capable of maintaining the angiogenic phenotype of ECs in an autocrine and paracrine manner (Nör et al., 2001; Heidemann et al., 2003). In addition, the activation of CXCR4 also results in NF- κ B translocation in glioma cells, which elicits the production of other angiogenic chemokines, such as CXCL1, CXCL2, and CXCL5 (Richmond et al., 2002). Therefore, glioma angiogenesis is the result of a well-coordinated process participated in by multiple angiogenic factors among which CXCR4 appears to be an upstream initiator.

3.3.3 CXCR4/CXCL12 mediates vasculogenesis by mobilizing bone marrow derived progenitor cells

In addition to tumor angiogenesis, which is thought to be established by the sprouting of blood vessels through the division of normal differentiated host ECs present in the tissue adjacent to tumor, another way to generate tumor vessels is through the process of vasculogenesis, which is formed by the recruitment of circulating EC precursor cells or bone marrow-derived cells (BMDCs) (Garcia-Barros et al., 2003). Circulating EC progenitor cells mobilized from the bone marrow are normally present in the peripheral blood of several species and participate in the neovascularization in tumor and in ischemic tissues (Spaeth et al., 2009). CXCR4 has been demonstrated to guide prime stem cells to the sites of rapid vascular expansion during embryonic organogenesis (Napoli et al., 2010). The pivotal role of CXCR4 and its ligand CXCL12 in vasculogenesis has been demonstrated in gene deletion mice as discussed earlier.

Similar to the development of embryonic vessels, CXCR4 mediates tumor neovascularization by switching from angiogenesis in the recurrent malignant glioma to vasculogenesis. For instance, tumor growth supported mainly by angiogenesis from nearby normal vessels is abrogated by irradiation (Kioi et al., 2010). As a consequence, the growth of new tumor vasculature in irradiation animals will rely mainly on circulating blood EC progenitor cells from the bone marrow. Studies have demonstrated that CXCR4 is a key factor for the influx of BMDCs into the recurrent tumor after irradiation, since both the CXCR4 inhibitor AMD3100 and antibodies against CXCR4 are able to block the recruitment of BMDCs into tumor and prevent the restoration of the vasculature (Kioi et al., 2010). Hypoxia also mediates tumor vasculogenesis through CXCR4 in animal models. Irradiation results in a hypoxic microenvironment in the tumor resulting in the up-regulation of the transcription factor HIF-1 (Ahn and Brown, 2008) and enhanced production of CXCL12 and VEGF. CXCL12 then induces the homing of CD11b⁺ BMDCs into the tumor site to initiate the formation of new vasculature (Kioi et al., 2010).

4. CXCR7/CXCL12

4.1 CXCR7 expression in glioma

Although it was believed that CXCL12 uses CXCR4 as a sole receptor, recent studies have shown that CXCR7, a newly identified chemokine GPCR, acts as an alternate receptor for

CXCL12 and for another chemokine e.g. interferon-inducible T cell α chemoattractant (I-TAC; also known as CXCL11). CXCR7 is expressed in several tumors and plays an important role in preventing tumor cell apoptosis and promoting tumor cell adhesion to ECs, a key step for the development of blood-borne metastasis (Burns et al., 2006). In glioma specimens, CXCR7 is widely distributed in tumor cells, microglia and ECs. In contrast, CXCR4 seems to be restricted to certain subsets of glioma cells and tumor stem-like cell populations. While the CXCR4 level is significantly higher in GBM than in lower grade gliomas, no distribution difference was detected for CXCR7 (Hattermann et al., 2010). One study reported that in eight glioma cell lines tested, only one expresses CXCR4. However, CXCR7 is highly expressed in all glioma cell lines (Hattermann et al., 2010). Interestingly, tumor stem-like cells derived from GBM cell line express CXCR4, but not CXCR7. In addition, differentiated glioma cells often are found to express CXCR7, but not CXCR4. These observations suggest that there is a difference between the role of CXCR4 and CXCR7 in the function of glioma cells. In some tumors, CXCR7 and CXCL12 are co-localized and potentially cooperate in tumor progression (Hattermann et al., 2010).

4.2 CXCR7 may mediate glioma progression

Initially, CXCR7 was regarded as a decoy receptor that recognizes CXCL12 or a coreceptor that may form a heterodimeric complex with CXCR4 to enhance CXCL12 signaling in embryonic cells. Subsequently, CXCR7 was demonstrated to be functionally active in glioma cells. CXCR7 activation by CXCL12 stimulates a transient phosphorylation of ERK1/2 and inhibits the apoptosis of glioma cells induced by camptothecin and temozolomide, but did not increase tumor cell proliferation and migration (Hattermann et al., 2010). CXCR7 activation also did not elicit calcium mobilization in tumor cells, but increases their adhesion (Burns et al., 2006). The absence of ligand-induced calcium influx and cell migration distinguishes the CXCR7 signaling pathway from CXCR4 and other typical chemokine GPCRs. In cells transiently transfected with human CXCR7 and rat cells expressing CXCR7, the signaling of CXCR7 is not mediated by Gai protein, but by β -arrestins associated with the phosphorylation of MAP kinases (Rajagopal et al., 2010). Based on these properties of CXCR7, it is assumed that some of the previously reported effects of CXCL12 on glioma cells, such as phosphorylation of kinases and prevention of apoptosis might be partially mediated by CXCR7. Since ECs isolated from GBM express high levels of CXCR7 mRNA, it is postulated that CXCR7 may be involved in the formation of glioma vasculature (Takano et al., 2010). Indeed, in many CXCR7⁺ tumors, VEGF and CXCL8 (IL-8) are up-regulated. Therefore, CXCR7 is a novel chemokine GPCR that promotes glioma progression by supporting tumor cell survival, adhesion and possibly vessel formation.

4.3 Potential interactions between CXCR7 and CXCR4

Accumulating evidence suggests that CXCR7 and CXCR4 interact with each other in malignant tumors. In human rhabdomyosarcomas (Grymula et al., 2010), downregulation of CXCR7 expression by hypoxia was thought to increase CXCL12 signaling through CXCR4 thus rendered rhabdomyosarcoma cells more motile and prone to detach from the primary tumor. Confocal microscopy shows that in glioma cell lines, CXCR7 is mainly localized in the space between the plasma membrane and endosomal compartment, whereas CXCR4 is mostly present on the cell surface of membrane (Calatuzzolo et al., 2011). The biological significance of the distinct pattern of CXCR7 and CXCR4 expression in glioma cells is not clear. However, in somatic cells, CXCR7 facilitates CXCR4-mediated migration of

primordial germ cells by controlling the level of CXCL12 in the microenvironment to form a chemotactic gradient (Boldajipour et al., 2008). In HeLa cells, CXCR7 acts as a scavenger receptor for CXCL12, which results in the internalization of CXCL12 and the subsequent reduction of CXCR4 activity (Naumann et al., 2010). An alternative mechanism by which CXCR7 regulates CXCR4 activity may be its potential to form heterodimer with CXCR4. In fact, some studies have shown changes in CXCR4 signaling by heterodimerization with CXCR7. Although the precise mechanisms of interaction between CXCR7 and CXCR4 and the consequences in glioma progression remain to be determined, the available results suggest an important role for CXCR7 in regulating the activity of the more ubiquitously expressed CXCR4 in gliomas (Fig. 1B).

5. CX3CR1/CX3CL1 in glioma progression

Another chemoattractant GPCR CX3CR1 and its agonist CX3CL1 have also been reported to play a role in glioma progression. CX3CL1 is one of the most highly expressed chemokines in the brain (Bazan et al., 1997) and is a peculiar member of the chemokine family which can mediate both chemotaxis and adhesion of inflammatory cells via its highly selective receptor CX3CR1. CX3CR1 is overexpressed in gliomas at both mRNA and protein levels, regardless of tumor classification and clinical severity, while CX3CL1 expression is correlated with glioma grade and overall patient survival (Locatelli et al., 2010). CX3CL1 is more highly expressed in tumor area near sites of necrosis suggesting that necrosis may directly enhance CX3CL1 transcription in tumor cells, or indirectly via inflammatory cytokines released by necrotic cells, including TNF α , which is a potent stimulant of CX3CL1 transcription (Marchesi et al., 2010). The increased expression of CX3CL1 in higher grade gliomas implies the involvement of CX3CL1 and its receptor CX3CR1 in tumor progression. CX3CR1 and CX3CL1 contribute to glioma progression in two ways: (1) by affecting the host defense mediated by immune cells and (2) by directly promoting tumor cell proliferation.

5.1 The role of CX3CR1 in immune cell activation in the brain

In colorectal cancer patients, high expression of CX3CR1 in tumor tissue is correlated with increased density of tumor infiltrating lymphocytes, which is associated with more favorable prognosis (Dimberg et al., 2007). CX3CR1 deficient mice bearing B16 melanoma are reported to show increased lung tumor metastasis and cachexia as well as reduced recruitment of monocytes and NK cells into the tumor (Yu et al., 2007). Thus, CX3CR1 may promote the infiltration of immune cells with antitumor activity.

Glioma-infiltrating microglia/macrophages (GIMs) are the major component in the stroma of glioma tumors and these cells express CX3CR1. *In vitro*, activation of CX3CR1 in GIMs isolated from human glioma specimens increases these cell adhesion and migration in response to CX3CL1 (Held-Feindt et al., 2010). Blocking CX3CR1 by a specific antibody reduced the migration of GIMs in response to the conditioned medium containing CX3CL1 secreted by human GBM cell lines (Held-Feindt et al., 2010). However, GIMs in glioma stroma did not mediate antiglioma immune responses (Liu et al., 2008). In fact, GIMs are characterized by a phenotype that may potentially promote tumorigenesis, i.e., more likely functioning as type II macrophages. Also, CX3CR1 activation increases the expression of MMP2, 9 and 14 in GIMs, which may not only favor the migration and adhesion of GIMs, but also the infiltration of normal brain tissue by tumor cells (Markovic et al., 2005).

5.2 The direct effect of CX3CR1 on glioma cells

Since CX3CL1 and CX3CR1 are co-expressed by glioma cells, they are hypothesized to play a role in glioma growth in an autocrine loop. However, the interaction of CX3CR1 with

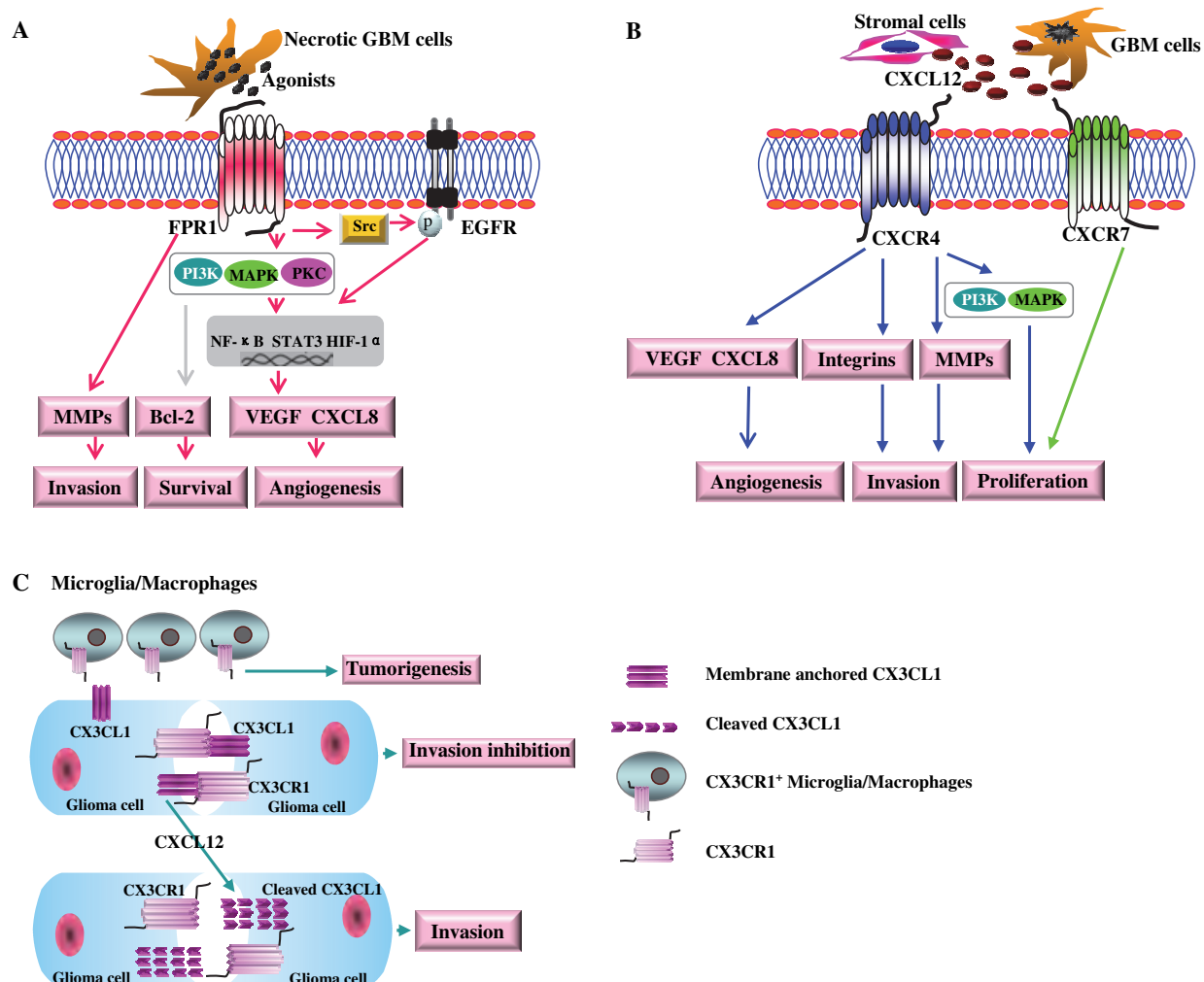


Fig. 1. The role of chemoattractant GPCRs in glioma progression. A. FPR1 and EGFR cooperate to exacerbate the progression of GBM. FPR1 in GBM cells was activated by agonists released by necrotic tumor cells to promote GBM cell survival, invasion and angiogenesis. The FPR1 function in GBM cells is mediated in part by transactivation of EGFR through a Src kinase pathway. B. Interaction of CXCR4 with CXCL12 produced by glioma cells and stromal cells promotes the proliferation, invasion and angiogenesis of tumor. The activity of CXCL12 may be partially mediated by another CXCL12 receptor CXCR7. C. CX3CL1 secreted by glioma cells increases the infiltration of microglia/macrophages expressing CX3CR1 and promotes tumor progression. Interaction of CX3CR1 with CX3CL1 produced by glioma cells increases cell-cell adhesion in tumor that inhibits the invasion of tumor cells. However tumor cells activated by CXCR4 ligand CXCL12 cleave CX3CL1 that increases the invasiveness of the individual tumor cells.

CX3CL1 has been shown to inhibit glioma cell invasion in vitro (Sciumè et al., 2010). This activity of CX3CR1 may be attributed to the peculiar structure of the agonist CX3CL1 and may account for its ability to directly promote cell-cell adhesion when expressed as a

transmembrane protein therefore impeding cell motility. The effect of this CX3CR1 and CX3CL1 interaction was reduced by TGF- β 1 (Sciumè et al., 2010), which is also produced by glioma cells and downregulates CX3CL1 expression. The *in vivo* role of CX3CR1 in glioma growth is more complex. CXCL12 constitutively expressed in the central nervous system (CNS) activates CXCR4 in glioma cells to promote the cleavage of CX3CL1 into a soluble form that reduces the intercellular adhesion and results in the dissemination of glioma cells (Cook et al., 2010). Thus, it is postulated that CX3CR1 in the CNS may favor the invasion of glioma cells into neighboring tissues. In support of this assumption, CX3CR1 and CX3CL1 have been reported to drive the neurotropic cancer cells to disseminate to peripheral nerves (Marchesi et al., 2010), a distinct but largely under appreciated route of metastasis, which has been shown in several tumors, including tumors of the brain, prostate, stomach, pancreas, bladder, and colorectum, as well as head and neck carcinoma. Thus, the balance between the transmembrane and soluble form plays an important role in the activity of CX3CL1 to either prevent or promote glioma progression (Fig. 1C).

6. Involvement of chemoattractant GPCRs in infiltration of gliomas by regulatory T cells (Tregs)

Tregs have been recognized as one of the major immune cell components that suppress host anti-tumor responses. Recruitment of Tregs into tumors contributes to tolerance by suppressing autoreactive T cells. It has been shown that Tregs infiltrate human brain tumors (Tran Tang et al., 2010) and preferentially accumulate in high grade malignant gliomas such as GBM. The importance of Tregs in the control of anti-tumor immune responses in experimental mouse glioma models is demonstrated by the observation that transient Treg depletion markedly augments the anti-tumor immunity (Tran Tang et al., 2010). Treg trafficking *in vivo* is facilitated by chemokine receptors. For instance, Treg accumulation in ovarian carcinoma is mediated by the chemokine receptor CCR4, which binds the ligand CCL22 produced in the tumor where specific T cell immunity is compromised (Curiel et al., 2004). Analysis of lymphocyte subsets in GBM from patients shows that tumor infiltrating Tregs highly express CCR4 (Jacobs et al., 2010) and the ligand CCL22 is produced by GBM cells. But unlike ovarian carcinoma in which Treg accumulation clearly correlates with reduced patient survival, there is no correlation between Tregs and overall survival of GBM patients. Regardless, post-surgical immunotherapy has been proposed as a potentially valid method to eliminate residual GBM cells while preserving surrounding healthy brain cells.

7. Chemoattractant GPCRs in gliomas as potential therapeutic targets

Given the broad range of functions of chemoattractant GPCRs in malignant glioma development, progression, invasion and angiogenesis, blockage of these receptors is considered a novel therapeutic approach in conjunction with conventional surgical resection, irradiation and chemotherapy. Based on the association of CXCR4 with the malignant behavior of glioma, anti-CXCR4 monoclonal antibody and specific low-molecular weight antagonist for CXCR4 have been tested for their effects on tumor cell growth *in vitro* and *in vivo*. As predicted, anti-CXCR4 monoclonal antibody is able to attenuate the migration and proliferation of human GBM cells induced by CXCL12 (Cheng et al., 2009). In addition, administration of the CXCR4 antagonist AMD3100 suppressed the growth of

xenograft tumors formed by human GBM cells transplanted intracranially into mice, with increased apoptosis of the transplanted GBM cells (Rubin et al., 2003).

Studies have also revealed the potential benefit of a combination of CXCR4 inhibitor with chemotherapy and radiotherapy in malignant glioma patients. In tests on a variety of GBM cell lines, a conventional cytotoxic chemotherapeutic agent, BCNU, in combination with the CXCR4 antagonist AMD3100 exhibits synergistic inhibition of tumor cell growth *in vitro*. *In vivo* in animal models, subtherapeutic doses of BCNU and AMD3100 also result in tumor regression, which is attributed to increased tumor cell apoptosis and decreased proliferation (Redjal et al., 2006). These effects of AMD3100 in conjunction with its capacity to reduce the recruitment of bone marrow EPCs to recurrent tumors post irradiation, suggest that targeting CXCR4 may not only directly inhibit tumor cell proliferation, but also indirectly abrogates neovascularization in GBMs (Kioi et al., 2010).

Considering targeting CXCR4 as a means of inhibiting glioma, the ability of the CXCR4 agonist CXCL12 to activate CXCR7 casts doubts about whether blockage of CXCR4 alone is sufficient without simultaneously inhibiting CXCR7. In fact, inhibition of CXCR4 only partially decreases the responsiveness of tumor cells to CXCL12 in several animal models. Studies have found that GSLCs express high levels of CXCR4 and low levels of CXCR7 (Hattermann et al., 2010). In contrast, differentiation of GSLCs markedly decreased CXCR4 expression but up-regulated CXCR7. It is therefore postulated that CXCR4 may mediate GSLC chemotaxis and survival, whereas differentiated glioma cells are protected from apoptosis by CXCR7 in response to CXCL12. It is therefore important to design strategies that target one or both CXCL12 receptors based on the stages of glioma cell differentiation.

Small molecule natural compounds constitute another source of inhibition of chemoattractant GPCRs with therapeutic potential for gliomas (Ping et al., 2007). One of such compounds is Nordy, a chiral mimetic of a natural lipoxygenase inhibitor nordihydroguaiaretic acid. Nordy has been shown to exhibit a broad inhibitory activity on chemoattractant GPCRs such as CXCR4 and FPR1 on GBM cells by downregulating receptor expression, interfering with their signal transduction pathways and reducing tumor cell production of angiogenic factors VEGF and the chemokine CXCL8 (Ping et al., 2007; Chen et al., 2006 and 2007). In addition, Nordy has been found to inhibit GBM cell proliferation and to promote tumor cell differentiation into a lesser malignant phenotype. Recently, Nordy was found to inhibit the self-renewal of glioma stem cells and growth of xenografts generated by the stem cells (Wang et al., 2011). However, the effect of Nordy may not be specific by targeting only chemoattractant GPCRs on GBM cells. Further studies are required to identify more specific receptor targeting natural compounds with minimal side effects on key physiological cell processes.

8. Conclusions

There is now mounting evidence that chemoattractant GPCRs play multiple roles in the progression of malignant gliomas, by mediating the tumor cell growth, invasion and angiogenesis (Table 1). However, further molecular epidemiologic and genetic studies are required to obtain a better understanding of the mechanisms of the function of these receptors in glioma cells. It is especially important not to single out a given receptor to study glioma biology, but rather, studies should consider the complex host environment in which many factors may drive the aberrant expression of chemoattractant GPCRs and ligands. In addition, the interaction of chemoattractant GPCRs such as CXCR4 and FPR1 with other

growth factor receptors has been reported and in fact different types of the receptors cooperate to exacerbate the progression of malignant glioma. In addition to their direct effect on glioma progression, chemoattractant GPCRs expressed on immune cells also mediate host response to tumors by promoting recruitment of “suppressive” leukocytes including myeloid suppressor cells, type II macrophages and Tregs into the tumor and peripheral lymphoid organ to compromise anti-tumor defense. Therefore, recognition of the multifaceted role of chemoattractant GPCRs in gliomas and other malignant tumors in general is fundamental to elucidating the mechanisms of tumor progression and the development of novel therapeutic agents.

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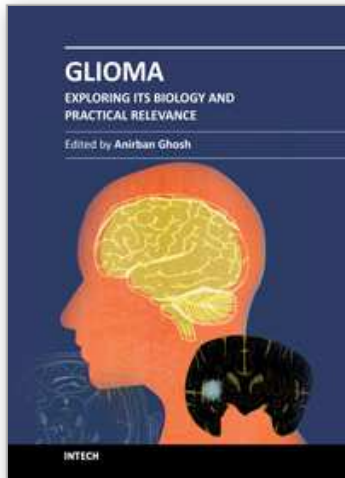
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The title 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

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