Contribution of SDF-1 α /CXCR4 Signaling to Brain Development and Glioma Progression

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Key Words

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Abstract

The SDF-1 α /CXCR4 signaling maintains central nervous system homeostasis through the interaction with the neurotransmitter and neuropeptide systems, the neuroendocrine systems. Recently, the SDF-1 α /CXCR4 signaling has been reported to present nonrandom distribution in brain development and glioma progression, which exerts differential regulations on the assembly, differentiation, and function of neural precursors, neurons, glial cells, as well as glioma cells. In the present review, we highlight current knowledge about multiple molecular signaling pathways associated with the SDF-1 α /CXCR4 signaling in glioma. Not only is the expression of CXCR4 a key determinant of glioma progression, but SDF-1 α is essential for site-specific invasive or metastatic processes. SDF-1 α is the switch of the SDF-1 α /CXCR4 signaling from the endocrine loop to the autocrine and/or local paracrine loop in glioma progression and brain development. Studies of SDF-1 α /CXCR4 signaling in the field of brain development may provide valuable tactics for glioma treatment.

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Introduction

Chemokines are small (8–14 kDa), secreted chemotactic proteins which are now the largest known cytokine family. Chemokines are classified into four subfamilies depending on the spacing of their first two cysteine residues: C, CC, CXC, and CX3C. Stromal cell-derived factor 1 α (SDF-1 α), also known as chemokine ligand 12 (CXCL12), is the only known ligand for G-protein-coupled, seven-span transmembrane chemokine receptor 4 (CXCR4) [1]. CXCR4 is also a target for human immunodeficiency virus (HIV) binding. The SDF-1 α /CXCR4 signaling mediates many physiological processes including cell trafficking, angiogenesis, and embryogenesis. It controls the chemotaxis of hematopoietic stem cells homing to the bone marrow in adults. Recently, it has been established that this signaling is playing a critical role in tumor invasion and metastatic processes. CXCR4 is highly expressed on a number of cancer cells, including human lung, breast, melanoma, and colon cancer cells [1–4]. SDF-1 is also constitutively secreted in a variety of tissues representing the first destinations of tumor metastasis such as lung, liver, lymph node, bone marrow, and adrenal gland [2, 5]. CXCR4 signaling in response to CXCL12 mediates actin polymerization and pseudopodia forma-

tion through calcium mobilization, β -arrestin recruitment, as well as ERK1/2 phosphorylation [2, 6].

SDF-1 has three isoforms, α , β , and γ , which are different at the splicing level, not at the transcriptional level [7]. In adult rat brain, SDF-1 α is the predominant one, present in astrocytes, microglia, as well as in neurons [8, 9]. Banisadr et al. [8] reported that SDF-1 α is found positive in normal cholinergic neurons, such as in the medial septum and substantia innominata, and in dopaminergic neurons, such as in the substantia nigra (SN) pars compacta and the ventral tegmental area.

CXCR4 is also present in astrocytes, microglia, and in neurons. CXCR4 is constitutively expressed in cholinergic, dopaminergic, and GABAergic neurons [10, 11]. Although CXCR4 is widely expressed in neurons in the neocortex, hippocampus, basal nuclei, thalamus, brain stem, and cerebellum [12], the areas of highest expression are subcortical regions and the limbic system [13]. As the limbic system has memory function, CXCR4 – the major co-receptor for the HIV-1 glycoprotein 120 (gp120) – plays a vital role in the development of HIV-related dementia [13, 14]. Van der Meer et al. [15] reported that the onset time of CXCR4 expression is between 3.5 and 4.5 years in the fetal human brain. Ligand-dependent or -independent internalization of CXCR4 is regulated by a C-terminal cytoplasmic domain between amino acids 336 and 342 [16]. CXCR7 has recently been identified as another receptor for SDF-1 α [17]. Further study is needed about the relationship between CXCR4 and CXCR7, cooperative or independent in SDF-1-dependent neuronal development [18].

Neuropathological Aspects of the SDF-1 α /CXCR4 Axis in Glioma

Prevalence and Histopathological Features in Glioma

We used both semiquantitative RT-PCR and real-time quantitative RT-PCR assays to determine mRNA expressions of CXCR4 and SDF-1 α in 76 astrocytomas and 10 normal brain tissues [19]. All of the astrocytomas exhibited high CXCR4 mRNA levels compared with normal brain samples. Moreover, the expression of CXCR4 increased with increasing tumor grades. Sehgal et al. [20] reported that CXCR4 was overexpressed in glioblastoma multiforme (GBM), with 57% of the primary specimens and 88% of the cell lines. CXCR4 protein expression is significantly higher in gliomas of grade III and IV than in gliomas of grade II [21, 22]. Our results, together with recent findings [22–25], manifested that CXCR4 expres-

sion correlates directly with the degree of glioma malignancy. Additionally, glioma cells with overexpression of CXCR4 were observed to develop rapidly growing and lethal xenografted tumors in mice [25]. Furthermore, CXCR4 is also related with angiogenesis and vasculogenesis. CXCR4 expression is observed in neovessel endothelial cells [21]. Primary human glioma samples with overexpression of CXCR4 showed high-density microvessels [25]. Patients with CXCR4-positive tumors demonstrated a lower rate of 3-year postoperative survival than those with CXCR4-negative tumors [25].

Although most gliomas exhibit CXCR4 expression, only part of the gliomas, especially high-grade gliomas, exhibit positive expression of SDF-1 α . Barbero et al. [26] reported that CXCR4 was expressed in all tumors analyzed, while SDF-1 α was expressed only in two tumor tissues. SDF-1 α expression increases with tumor grade [21]. In our study [19], 16 samples of WHO grade II exhibited no expression of SDF-1 α mRNA, while 90.0% of GBMs exhibited high expression of SDF-1 α . The overexpression of SDF-1 α is evident mainly in the pseudopalisading cells and the proliferating microvessels [27]. In low-grade gliomas, positive expression of SDF-1 α protein is a predictive factor for a significantly shorter time to tumor progression [28, 29]. Also, in 40 low-grade oligodendrogliomas and oligoastrocytomas, the prognostic value of SDF-1 α expression, either on tumor or on endothelial cells, is associated with a significantly shorter time to tumor progression [30]. SDF-1 α mediates normal structure formation, as shown in the brain development discussed below. Furthermore, SDF-1 α also takes part in maintaining the blood-brain barrier. SDF-1 α plays an anti-inflammatory role, which limits inflammation by localizing mononuclear infiltrates to the perivascular space [31]. In addition, SDF-1 α stimulates brain capillary endothelial cells to tube-like structure formation [32].

There is a marked co-localization of CXCR4 and SDF-1 α in tumor cells, especially in regions of angiogenesis and degenerative, necrotic, and microcystic changes, which demonstrates the close relationship with angiogenesis and immune response [21, 33]. Additionally, GBM cells exhibited low expression of SDF-1 α /CXCR4 in an aerophilic condition and a high expression of SDF-1 α /CXCR4 in a hypoxic condition [27].

Interestingly, the SDF-1 α /CXCR4 signaling also mediates the nonrandom formation of Scherer's secondary structures, which is unique in GBM patients [34]. CXCR4 was widely expressed in tumor cells around neurons and blood vessels. SDF-1 α , unlike CXCR4, was selectively expressed in Scherer's secondary structures, namely neu-

rons, blood vessels, subpial regions, and white matter tracts [34]. Not only is the expression of CXCR4 a key determinant of tumor progression, but SDF-1 α is also essential for site-specific invasive or metastatic processes [4, 35–37]. Although tumor cells showed low levels of SDF-1 α expression as compared with CXCR4, SDF-1 α exhibits peak levels of constitutive expression in regions or organs representing the first destination of cancer invasion or metastasis [4, 34–37]. Previous studies have demonstrated that recombinant human SDF-1 α could stimulate the proliferation of a variety of tumor cells in vitro [38, 39]. But re-expression of endogenous SDF-1 α in colorectal or breast carcinoma cells inhibited metastatic tumor formation in mice [4, 37]. SDF-1 α expression in tumor cells, in summary, is the switch of the SDF-1 α /CXCR4 signaling from the endocrine loop to the autocrine and/or local paracrine loop. Cancer cells, lacking expression of SDF-1 α but maintaining expression of CXCR4, follow the endocrine SDF-1 α gradients to remote regions. Cancer cells, maintaining expression of SDF-1 α and CXCR4, dwell and proliferate in the primary region, in the autocrine and/or local paracrine loop.

Roles of SDF-1 α /CXCR4 in Brain Development

Neurogenesis occurs only in discrete regions of the adult brain: the subventricular zone (SVZ) and the subgranular zone [40]. During brain development, SDF-1 α exerts differential regulation on distinct cell populations, including neuronal progenitor and precursor cells, glutamatergic and GABAergic neurons, and glial cells [41]. Tissir et al. [42] studied the expression of CXCR4 and SDF-1 α mRNA during mouse brain development. CXCR4 is widely expressed in neuronal progenitor cells and subpopulations of differentiating neurons, including cerebellar external granule cells, cranial nerve nuclei, and telencephalic preplate. But CXCR4 expression tapers off during brain development. In contrast, SDF-1 α expression is scattered only in the telencephalic intermediate zone in embryos and in the meninges in adults [42].

Neuronal Precursor Cells

Neural stem cells (NSCs) are a subset of self-renewing and multipotent neural progenitor cells (NPCs) that generate the main phenotypes of the nervous system. Among the various chemokine receptors in adult mouse NSCs, CXCR4 exhibits the highest mRNA levels and functionality in chemotaxis assays and calcium signaling experiments [43]. SDF-1 α induces human NPC migration

through upregulation of inositol 1,4,5-triphosphate, extracellular signal-regulated kinases (ERK) 1/2, Akt, c-Jun N-terminal kinase, and intracellular calcium and down-regulation of cAMP [44]. Although the SDF-1 α /CXCR4 signaling promotes the migration of NPCs, it reversibly prevents NPCs from proliferation, keeping NPCs in a quiescent state [45]. SDF-1 regulates the proliferation of progenitors, possibly through a mechanism involving connexin 43-mediated intercellular coupling [41]. Li et al. [46] demonstrated that SDF-1 α alone could neither stimulate the self-renewal of NPCs, nor enhance bFGF/EGF-induced proliferation of NPCs. But the CXCR4 antagonist AMD3100 blocks the bFGF/EGF-induced expansion of NPCs through modulating their cell cycling.

The SDF-1 α /CXCR4 signaling directly regulates the migration of neuronal precursor cells, including cortical Cajal-Retzius cells, cerebellar granule precursor cells and dentate gyrus (DG) granule precursor cells [47]. (1) Cajal-Retzius cells are reelin-producing neurons, located in the human embryonic deep marginal zone. SDF-1 α secreted by the leptomeninges is indispensable to the tangential migration of Cajal-Retzius cells along the cortical surface [48, 49]. Mutations in CXCR4 result in Cajal-Retzius cells ectopically placed in the deeper cortical layers during neocortical development [49]. However, Stumm et al. [50] argued that SDF-1 α in the leptomeninges does not selectively regulate Cajal-Retzius cells, but regulates interneuron precursor migration from the basal forebrain to the neocortex. In the postnatal CA1 stratum lacunosum-moleculare, SDF-1 α suppresses spontaneous firing in Cajal-Retzius cells via hyperpolarization, which is involved in the information processing of the stratum lacunosum-moleculare [51]. (2) The SDF-1 α /CXCR4 signaling also promotes the migration of cerebellar granule precursor cells from the upper rhombic lip and the external germinal layer to the internal granular layer, as well as the proliferation of granule cells [52–54]. Silencing of the SDF-1 α gene results in loss of external germinal layer cells' chemotactic ability in the meninges. This suggests the predominant role of SDF-1 α in cerebellar neuronal migration [52]. (3) In DG development, SDF-1 α directly attracts DG progenitor migration, especially first to a transient subpial neurogenic zone [55, 56]. In mice deficient in CXCR4, mitotic cells in the migratory stream and in the DG are decreased, and neurons differentiate prematurely before reaching their target [57]. However, Li et al. [56] found that the final settlement of the DG granule precursor cells at the subgranular zone is not dependent on the SDF-1 α /CXCR4 signaling. In addition, SDF-1 α guides the growth of perforant fibers linking the entorhinal cor-

tex with the DG in a neural circuit [58]. During the early postnatal period, SDF-1 α is expressed in Cajal-Retzius cells on the upper and lower blades of the dentate and in the maturing dentate granule neurons, as well as in the meninges [59]. Bhattacharyya et al. [60] observed that SDF-1 α regulates GABAergic inputs from basket cells to the pool of dividing NPCs in the postnatal DG.

Glutamatergic and GABAergic Neurons

Functioning of the cerebral cortex requires the coordinated assembly of two classes of cortical neurons: excitatory projection neurons (e.g. glutamatergic neurons) and inhibitory local circuit neurons (e.g. GABAergic interneurons) [61]. Cortical glutamatergic neurons derive from the ventricular zone (VZ) of the dorsal telencephalon, while 65% of cortical GABAergic neurons (Dlx1/2-positive and Mash1-positive) derive from the VZ and SVZ of the dorsal forebrain, and the other 35% (Dlx1/2-positive and Mash1-negative) derive from the ganglionic eminence of the ventral forebrain [62, 63]. The SDF-1 α /CXCR4 signaling regulates these highly stereotyped routes. SDF-1 α /CXCR4 also mediates the interaction between glutamatergic neuron precursors and GABAergic interneurons in the intermediate zone (IZ)/SVZ [64]. In addition, CXCR4 promotes neuronal survival by inhibiting the E2F-dependent apoptotic pathway, maintaining neurons in a highly differentiated and quiescent state [65].

GABAergic interneurons are divided into several subtypes, according to their expression of parvalbumin, calbindin, calretinin, and somatostatin [66, 67]. CXCR4 is required for the proliferation, differentiation, and layer-specific distribution of interneuron subtypes [41, 66]. Constitutive deletion of CXCR4 signaling leads to disorganized migratory streams and premature cortical plate invasion of GABAergic interneurons, which disrupts their laminar and regional distribution [61, 66, 68]. In the developing telencephalon, cortical GABAergic neurons require SDF-1 α to maintain their tangential migration to the IZ/SVZ [69, 70]. During invasion of the cortical plate, these neurons change the tangential course to the radial one, accompanied by a decrease of SDF-1 α in the IZ/SVZ [68, 69]. In addition, SDF-1 α /CXCR4 increases the production and neurite localization of GABA and promotes the maturation of GABAergic neurons through downstream activation of ERK1/2, Egr1, and GAD67 (a 67-kDa form of glutamic acid decarboxylase) [71].

SDF-1 α acts in the generation of axons and dendrites (fig. 1). In cortical glutamatergic neurons, SDF-1 α enables the elongation and branching of axons [41]. Simi-

larly, SDF-1 α regulates both path finding and elongation of axons in the developing hippocampus and cerebellum [72–74]. SDF-1 regulates axon development, without affecting the other neurites, via dendrite-selective trafficking of CXCR4 in endosomes [75]. At an early developmental stage of hippocampal neurons, CXCR4 at the leading edge of growing neurites stimulates axonal branching but reduces growth of cone number and axonal outgrowth. CXCR4 is broadly distributed along axons and dendrites during the maturation of neurons [73]. In cultured cerebellar granule neurons, a low concentration of SDF-1 α promotes axon elongation via the Rho/mDia pathway, while a high concentration of SDF-1 α inhibits axon elongation via the Rho/ROCK pathway [72]. In addition, SDF-1 α /CXCR4 is essential for placode assembly and sensory axon path finding in the olfactory system [76].

SDF-1 α modulates synaptic transmission and electrical activity. Limatola et al. [77] observed a pronounced expression of CXCR4 in cerebellar glial, granule, and Purkinje cells. SDF-1 α provokes Ca²⁺ transients in both granule cell bodies and neuronal processes. In Purkinje neurons, SDF-1 α triggers a slow inward current followed by an increase of both the intracellular Ca²⁺ level and spontaneous synaptic activity [77]. Also, in Purkinje neurons, SDF-1 α restrains evoked excitatory postsynaptic currents (EPSC) stimulated by the parallel fibers [78]. Interestingly, both activities of SDF-1 α mentioned above in Purkinje neurons are mediated by glutamate release from glial cells [77, 78]. However, Guyon et al. [79] reported that SDF-1 α directly modulates voltage-dependent currents of the action potential in mammalian neuronal cells. Furthermore, Liu et al. [80] found that synchronized spontaneous Ca²⁺ spikes among hippocampal neurons are suppressed by SDF-1 α through the inhibition of the cAMP pathway. Synchronized Ca²⁺ spikes, arising from periodic burst firing of action potentials, participate in the development and plasticity of neuronal circuitry [80]. Giant depolarizing potentials (GDPs) play a vital role in the establishment and maturation of synaptic connections during the early development of the hippocampus [81]. GABA has an excitatory action on GDPs, while glutamate has an inhibitory action on them. Kasiyanov et al. [82] found that SDF-1 α decreases GDP firing induced by GABA in the immediate postnatal period of the hippocampus. In newly formed DG granule cells, CXCR4 is tonically activated and downregulated by endogenous SDF-1 α , which is postulated to be important to neurogenesis-dependent long-term memory in the adult hippocampus [83].

Fig. 1. SDF-1 selectively regulates axon development (see [41, 72–75]).

In addition, the SDF-1 α /CXCR4 signaling is required for nuclei formation. Zhu et al. [84] showed that SDF-1 α regulates the migration of mossy-fiber projecting precerebellar neurons tangentially from the lower rhombic lip to the hindbrain, forming precerebellar nuclei. SDF-1 α also regulates the anteroventrally directed migration of the pontine neurons to the pons, forming the pontine nuclei [84].

Glial Cells

The SDF-1 α /CXCR4 signaling regulates migration and proliferation of oligodendrocyte precursors (OLPs) as well as neural precursors [85]. CXCR4 mediates migratory response of neonatal OLPs, which co-expresses with platelet-derived growth factor receptor- α (PDGFR- α). The expressions of CXCR4 and PDGFR- α receptors also decreases during OLP differentiation [85]. Further, SDF-1 α dose-dependently increases OLP proliferation and myelin production [86]. Multiple sclerosis is an autoimmune disease in which myelin sheaths around the axons are demyelinated with loss of oligodendrocytes. During demyelination, the activated astrocytes and microglia enhance the secretion of SDF-1 α , which in turn promotes the differentiation of OLPs into oligodendrocytes for remyelination [87].

CXCR4 is also widely expressed on glial cells, including astrocytes and oligodendrocytes. Astrocytes act as

structural and metabolic support for neurons. Their anatomical position between blood vessels and neurons makes them an interface for energy metabolism and neurotransmitter regulation [88, 89]. SDF-1 α stimulates a series of intracellular and extracellular events, such as the release of Ca²⁺, TNF- α , and prostaglandins, which eventually leads to glutamate release [88].

Roles of SDF-1 α /CXCR4 in Brain Function

SDF-1 α /CXCR4 Axis and Hypothalamus/Pituitary Axis

The interaction of SDF-1 α /CXCR4 plays an important role in the regulation of the hypothalamus/pituitary axis. CXCR4 is expressed in normal anterior pituitary, as well as in the hypothalamus. SDF-1 α stimulates both prolactin and growth hormone (GH) production, secretion, and cellular proliferation [90–92]. Barbieri et al. [90] and Florio et al. [91] found that the SDF-1 α -induced GH release is a solely Ca²⁺-dependent process, while SDF-1 α -induced proliferation of GH4C1 rat pituitary adenoma cells is dependent on both the Ca²⁺-independent stimulation of ERK1/2 activity and the Ca²⁺-dependent activation of Pyk2 and large-conductance Ca²⁺-activated K⁺ channels (BK_{Ca}).

Hypothalamic gonadotropin-releasing hormone (GnRH) neurons control pituitary gonadotropin secretion and gametogenesis. During development, these neurons migrate from the olfactory placode to the hypothalamus [93]. In the process, the SDF-1 α /CXCR4 signaling does not function as guidance in the directional outgrowth of olfactory axons, but it guides GnRH-1 neuronal migration and modulates GnRH-1 production in these neurons [94, 95]. Similarly, knockdown of SDF-1 α or CXCR4 in GnRH3 neurons of the zebrafish influenced GnRH3 neuron migration. It also altered directional outgrowth of neuronal axons, losing its characteristic lateral crossing at the anterior commissure and optic chiasm [93].

In the lateral hypothalamus, CXCR4 is found in neurons secreting melanin-concentrating hormone (MCH), which contributes to feeding behavior regulation [8, 96]. SDF-1 α may control MCH neuron excitability indirectly through glutamate/GABA release and directly through voltage-dependent membrane currents [96].

SDF-1 α /CXCR4 also takes part in the regulation of the hypothalamo-neurohypophyseal system. SDF-1 α is localized in the arginine vasopressin/antidiuretic hormone (AVP/ADH) neurons, including the hypothalamic supra-optic nucleus, the paraventricular nucleus, and the posterior pituitary [8, 97, 98]. SDF-1 α modulates central water balance through the electrophysiological activities of AVP/ADH neurons and consequently AVP/ADH release, but not dependent on peripheral modifications of kidney water balance [97, 98].

SDF-1 α /CXCR4 Axis and Nigrostriatal Dopamine System

Parkinson's disease (PD) is a degenerative disorder resulting from the death of dopamine-generating cells in the SN. However, the cause of cell death is unknown. Shimoji et al. [99] reported that the SDF-1 α /CXCR4 signaling is involved in the inflammation and proliferation of microglia, which may contribute to the death of dopamine-generating neurons. Furthermore, the pathological expression of SDF-1 α and CXCR4 in the SN of PD patients was much higher than in normal controls in spite of loss of dopamine neurons [99]. Skrzydelski et al. [100] used patch clamp to record the electrophysiological activities of dopamine neurons in the SN. SDF-1 α stimulated neurons to dopamine release by a depolarization and an increased action potential frequency as well as by a change from a tonic firing pattern of depolarization to a burst firing pattern. Guyon et al. [101] reported that SDF-1 α acts directly on the membrane conductance and

high voltage-activated Ca²⁺ currents of dopamine neurons in the SN. When Ca²⁺ currents were activated by the depolarization of KCl, lower SDF-1 α concentrations were needed for dopamine release. CXCR4 is also expressed on non-dopamine cells in the SN. In these cells, SDF-1 α indirectly stimulates dopamine neurons by pre-synaptic mechanisms, including an increased frequency of spontaneous and miniature GABA(A) postsynaptic currents, a glutamatergic inward current, and an outward G protein-activated inward rectifier current [102]. In addition, CXCR4 participates in the regulation of the striatal function. Trecki et al. [11] detected the co-localization of CXCR4 and D1 dopamine receptors by cholinergic and GABAergic neurons in the caudate putamen and lateral shell of the nucleus accumbens. Rats improved their behavior both in the cylinder test and amphetamine-induced rotation test after mesenchymal stem cell (MSC) transplantation [103]. Wang et al. [103] attributed the neuroprotective effects of MSC dopaminergic neurons partly to the anti-apoptotic effects of SDF-1 α .

SDF-1 α /CXCR4 Axis and Opioids/Cannabinoids

The SDF-1 α /CXCR4 signaling has also been confirmed to participate in heterologous desensitization. SDF-1 α can influence the pharmacodynamic action of neuronal active agents, such as the opioids and cannabinoids. A similar pattern of expression is found for CXCR4 and μ -, κ -, and δ -opioid receptors in the brain, including the cingulate cortex, hippocampus, and periaqueductal gray (PAG) [104–107]. As is known, the PAG is a brain region in charge of pain signal processes, a target which many analgesic compounds act on [108]. The SDF-1 α /CXCR4 axis expressed by the immune cells downregulates the electrophysiological activity of μ -, κ -, and δ -opioid receptors on the PAG [104, 109]. Although morphine reduces input resistance by hyperpolarization, SDF-1 α blocks morphine's electrophysiological effects on the PAG neurons [104]. Heterologous desensitization induced by SDF-1 α blocks the analgesic action of opioid receptors, which enhances the perception of pain at inflammatory regions [104, 107, 109]. However, this heterologous desensitization is bidirectional. Evidence demonstrates that opioid receptors are also able to cross-desensitize CXCR4 [107, 110]. Opioid receptors interact on normal CXCR4 receptors in different ways, depending on opioid receptors' subtypes [110]. In the control of bidirectional heterologous desensitization, apart from target receptor phosphorylation, the action of downstream signaling molecules, such as protein kinase A (PKA) or

PKC, inhibits the coupling of GPCRs with the target receptor [111]. Activation of SDF-1 α /CXCR4 in the PAG also interferes with the analgesic effects of the cannabinoid receptor agonist, an aminoalkylindole, WIN55,212-2 [112]. In addition, SDF-1 α blocks hypothermia induced by WIN55,212-2 in the preoptic anterior hypothalamus [113]. But such an effect does not extend to other opioid medications such as buprenorphine. The SDF-1 α /CXCR4 signaling does not influence the antinociceptive effect of buprenorphine. Conversely, buprenorphine appears to be more effective at high levels of SDF-1 α in neuroinflammatory conditions [108].

SDF-1 α /CXCR4 Axis and Serotonin System

The serotonin (5-hydroxytryptamine, 5-HT) system is closely related with depression. Over 70% of serotonin neurons co-localize with SDF-1 α and CXCR4 in the rat dorsal raphe nucleus [114]. SDF-1 α indirectly modulates 5-HT neurotransmission via presynaptic enhancement of GABA and glutamate release. SDF-1 α raises the frequency of spontaneous inhibitory and excitatory postsynaptic currents (sIPSC and sEPSC) as well as the amplitude of sIPSC in 5-HT neurons [114]. Further study about the relationship between the SDF-1 α /CXCR4 axis and the serotonin system may help cure depression associated with disorders of immune function.

Others

CXCR4 is also implicated in autonomic dysfunction, such as gastrointestinal dysfunction. Physiological studies [115] demonstrate that nano-injection of SDF-1 α into the dorsal vagal complex of the hindbrain resulted in a significant decrease of gastric motility. In the development of vertebrate central nervous system (CNS), SDF-1 α /CXCR4 helps direct the ventral axon trajectory of spinal motor neurons (vMN) [116]. In the absence of CXCR4, mice developed with impaired limb innervation and myogenesis [117].

Alzheimer's disease (AD) is a well-characterized disease with cognitive decline involving two classic abnormal structures called plaques and tangles. Reduced SDF-1 α levels were found in AD patients. Furthermore, the chronic treatment of SDF-1 α antagonist results in similar cognitive deficits as in AD [118]. Short-term exercise showed a significant increase in SDF-1 α , which may improve cognition [119]. In stroke, isoforms of SDF-1 play distinct roles during cerebral ischemia [120]. SDF-1 α /CXCR4 recruits stem cells from the peripheral blood and mediates the repair and neoangiogenesis of ischemia regions [121–123].

Molecular Signals Associated with the SDF-1 α /CXCR4 Axis in Glioma

SDF-1 α /CXCR4 Axis and VEGF

Neuronal cells increase SDF-1 α production upon the exposure of vascular endothelial growth factor (VEGF) [34]. VEGF induces SDF-1 α and CXCR4 production by endothelial cells, which bind angiogenesis and chemotaxis together [29, 34, 124, 125]. The interaction between SDF-1 α and CXCR4 in endothelial cells enlarges the process of angiogenesis by inducing more VEGF secretion [125–128]. VEGF expression also upregulates SDF-1 α and CXCR4 production in human glioma cells [129]. Interestingly, activation of chemokine receptor CXCR4 in malignant glioma cells also contributes to the high level of VEGF produced by malignant glioma cells [23]. These data exhibit a positive-feedback loop in which VEGF induces SDF-1 α and CXCR4 production by endothelial cells and glioma cells, and in turn the SDF-1 α /CXCR4 signaling magnifies VEGF expression by these cells (fig. 2). These findings suggest that the interaction between SDF-1 α /CXCR4 and VEGF might play a vital role in tumor vasculogenesis and angiogenesis.

SDF-1 α /CXCR4 Axis and HIF-1 α

The CXCR4 receptor was found co-localized with HIF-1 α in glioma cells around areas of necrosis, which suggested its correlation with hypoxia [124]. Hypoxia stimulates CXCR4 production by the activation of HIF-1 α in tumor cells and the secretion of VEGF in human brain microvascular endothelial cells (HBMECs) [124]. Loss of function of von Hippel Lindau (VHL), which is required for oxygen-dependent degradation of HIF-1 α , is associated with increased expression of CXCR4 and SDF-1 α [130]. The hypoxia-induced release of SDF-1 α is regulated not by p53, but by TGF- β -dependent HIF-1 α [131]. Hypoxia is a key factor in determining NSC tropism to glioma. Hypoxia enhances the self-renewal capacity and inhibits the differentiation induction of the CD133-positive human glioma-derived cancer stem cells through activation of HIF-1 α [132]. The SDF-1 α /CXCR4 signaling mediates increased NSC-to-glioma tropism under hypoxia [133].

SDF-1 α /CXCR4 Axis and TNF- α

The SDF-1 α /CXCR4 signaling controls glutamate release from astrocytes via TNF- α and subsequently regulates glia-glia and glia-neuron communication (fig. 3) [134, 135]. TNF- α , in turn, induces production of CXCR4 at both the mRNA and protein levels in human and sim-

Fig. 2. The positive feedback loop between SDF-1 α /CXCR4 and VEGF (see [23, 29, 34, 124–129]).

ian astrocytes as well as in glioma cells [136, 137]. With the cooperation of microglia, enhanced release of SDF-1 α -induced TNF- α forms an autocrine or paracrine loop, which may cause the derangement of glial communication [134]. As for human endothelial cells, TNF- α has a biphasic effect on CXCR4 expression, with early inhibition and late induction [138]. Furthermore, TNF- α augments expression of CXCR4 on bone marrow-derived hMSCs, which elevates SDF-1 α -induced migration of hMSCs to intracranial gliomas [139]. But Han et al. [140]

reported that CXCR4 expression is reduced by exposure to TNF- α in primary mouse astrocytes. These findings suggest that TNF- α might play multiple roles in the regulation of the SDF-1 α /CXCR4 axis among different cell types.

SDF-1 α /CXCR4 Axis and bFGF

CXCR4 is shown to be enhanced upon exposure to basic fibroblast growth factor (bFGF) in malignant glioma cells as well as in endothelial cells [141]. Conversely, SDF-1 α treatment inhibits the proliferation of endothelial cells induced by bFGF and prolongs the survival of endothelial cells [141]. These results suggested that the interaction of SDF-1 α /CXCR4 and bFGF may modulate the cross talk between glioma cells and endothelial cells.

SDF-1 α /CXCR4 Axis and Interleukins

The inflammatory cytokine IL-1 β has recently been reported to mediate pathologic relocation of SDF-1 α early before the disruption of the blood-brain barrier in multiple sclerosis [142]. In human astrocytoma cells, CXCR4 protein expression is increased after treatment of IL-1 β [136]. Secretion of IL-6 enhances surface expression of CXCR4 and subsequently promotes SDF-1-dependent chemotaxis in astrocytes, which is involved in reactive gliosis and HIV-related dementia [143]. On the other hand, SDF-1 α induces production of IL-8 in human astrocytoma cells [136]. Furthermore, CD133-positive glioma cells secrete more IL-8 than negative ones [144]. The lipoxygenase inhibitor Nordy, a synthetic chiral compound of nordihydroguaiaretic acid, diminishes CXCR4 expression in glioma cells and reduces tumor formation in mice [25]. In addition, Nordy significantly suppresses SDF-1 α -induced production of angiogenic factors, IL-8 and VEGF, in glioma [145].

SDF-1 α /CXCR4 Axis and C3a

Complement-derived anaphylatoxin C3a plays pathologically paradoxical roles in the CNS. C3a has anti-inflammatory functions, such as neurotrophin production and neurotoxicity prevention, as well as proinflammatory functions [146]. Furthermore, C3a also has physiological functions of neurogenesis and neuroprotection. Although C3a alone does not have a chemotactic ability in NPCs, it facilitates NPC migration at low levels of SDF-1 α , while it inhibits NPC migration at high levels of SDF-1 α [147]. Similarly, C3a restrains neuronal differentiation of NPCs in the presence of SDF-1 α , while it promotes NPC differentiation without SDF-1 α [147].

Fig. 3. SDF-1 α /CXCR4 axis and TNF- α (see [134–138]).

SDF-1 α /CXCR4 Axis and Matrix Metalloproteinases

SDF-1 α augments the expression of membrane type-2 matrix metalloproteinase (MT2-MMP), but not the other MT-MMPs, MMP-2 or MMP-9 [148]. The SDF-1 α -induced invasiveness of glioma cells is suppressed after silencing of MT2-MMP [148]. Leucine-rich repeats containing 4 (LRRC4) plays an inhibitory role on the progression of gliomas. Overexpression of LRRC4 inhibits SDF-1 α /CXCR4 downstream molecules, such as ERK1/2 and Akt, and then proMMP-2 activation [149].

SDF-1 α /CXCR4 Axis and Dipeptidyl Peptidases

Dipeptidyl peptidase-IV (DPP-IV, CD26) is a serine protease expressed on the surface of most cell types and is associated with immune regulation, signal transduction, and apoptosis. The increase of CXCR4 expression

parallels with the rise of DPP-IV expression and activity in higher-grade gliomas, which suggests a potential relationship between DPP-IV and SDF-1 α /CXCR4 [150]. Further studies [151, 152] demonstrated that CD26/DPP-IV has the ability to cleave SDF-1 α at its position 2 proline.

SDF-1 α /CXCR4 Axis and BDNF

Brain-derived neurotrophic factor (BDNF) downregulates the expression of CXCR4 in the brain by internalization [153, 154]. Furthermore, it is assumed that downregulation of CXCR4 partly explains the neuroprotective function of BDNF against HIV envelope protein gp120 toxicity [153, 154]. The modulatory role of BDNF in CXCR4 expression occurs only in mature animals [154].

SDF-1 α /CXCR4 Axis and HGF/c-Met Axis

Nuclear factor- κ B (NF- κ B) mediates a cross talk between the SDF-1 α /CXCR4 and HGF/c-Met axes in glioma migration [155]. SDF-1 α and CXCR4 production are enhanced upon exposure to hepatocyte growth factor (HGF) in glioma cells [156]. HGF-induced upregulation of SDF-1 α /CXCR4 occurs through a NF- κ B-dependent mechanism. HGF stimulates nuclear translocation of NF- κ B by phosphorylation and degradation of I κ B- α [155]. It is interesting to find that knock down of NF- κ B suppresses CXCR4 expression induced by HGF but not by hypoxia alone. But this suppression persists with hypoxia accompanied by HGF [155].

SDF-1 α /CXCR4 Axis and Fractalkine/CX(3)CL1

The chemokine fractalkine/CX(3)CL1 and its cognate receptor, CX3CR1, play a role in atherogenesis and neuroprotection. SDF-1 α increases cleavage of fractalkine from neurons through the stimulation of the inducible metalloproteinase ADAM-10 and -17 [157]. In addition, SDF-1 α also upregulates expression of the fractalkine gene [157]. It is assumed that the interaction between SDF-1 α and fractalkine contributes to neuroprotection of cortical neurons by modulating microglial neurotoxic properties [157].

SDF-1 α /CXCR4 Axis and Prostaglandins

The cross talk between SDF-1 α /CXCR4 and prostaglandins modulates the pathogenic network responsible for neuronal toxicity [158]. HIV-1 envelope gp120 stimulates cyclooxygenase (COX)-2 expression in astrocytoma cells via NF- κ B [159]. In human astrocytes, SDF-1 α induces production of COX-2 and secretion of prostaglandin E2 (PGE2) also via NF- κ B [158]. Culture supernatants from SDF-1 α -treated astrocytes inhibit viability of tumor cells, and COX inhibitors prevent this toxicity [158].

Others

Src homology 2 domain-containing phosphatase 2 (SHP2), encoded by PTPN11, is a non-receptor protein-tyrosine phosphatase. It is regarded as a proto-oncogene involved in tumor survival, proliferation, migration, and differentiation. SDF-1 α induces phosphorylation of the tyrosine phosphatase SHP2, which contributes to the guidance of granule cell migration during cerebellar development [160]. SDF-1 α induces plasminogen activator inhibitor-1 (PAI-1) expression in human glioma cells, which is required for activation of G α (i), ERK [161]. In addition, CXCR4 is repressed by the Notch ligand δ -like 4 (Dll4) in endothelial cells [162].

Signal Transduction of the SDF-1 α /CXCR4 Axis in Glioma

SDF-1 α /CXCR4 Axis and PI3K-AKT-ERK

SDF-1 α binding on the CXCR4 receptor activates both neurons and leukocytes through G(α i) activation [54]. Distinct from leukocytes, SDF-1 α -induced activity in neurons is involved in Ca $^{2+}$ flux, requiring depolarization by KCl or pretreatment by glutamate [54]. SDF-1 α provokes a raise of intracellular Ca $^{2+}$ concentration and rapid phosphorylation of the mitogen-activated protein kinase (MAPK) cascade, specifically, extracellular signal-regulated kinase ERK1/2 in glioma cells [136, 163, 164]. In primary cultures of rat type-I astrocytes, SDF-1 α selectively activates ERK1/2, but not p38 or stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) [165]. In these astrocytes, Pyk2 is regarded as an upstream component for the SDF-1 α /CXCR4 signaling to ERK1/2 [165]. As to the ERK pathway, there are different responses to SDF-1 α and the HIV glycoprotein gp120 in NPCs, neurons, and astrocytes [166]. In normal neurons, both SDF-1 α and gp120 could stimulate phosphorylation of ERK1/2, while in NPCs and astrocytes, kinase activation is only induced by SDF-1 α , but not gp120 [166]. In addition, SDF-1 α also stimulates focal adhesion kinase (FAK) and Akt [34, 164, 165, 167]. Although both ERK1/2 and Akt are coupled to CXCR4 in cerebellar granule neurons and neuroepithelioma cells, ERK1/2 activation shows a different dependency on the phosphatidylinositol-3 kinase (PI3K) pathway, suggesting that different G proteins are involved in these two cell systems [165, 168]. Furthermore, Floridi et al. [168] demonstrated that inhibition of either ERK or PI3K impedes the migration induced by SDF-1 α in neuroepithelioma cells, while only PI3K is indispensable for the migration of cerebellar granule neuron. In normal astrocytes, G-protein-PI3K-ERK1/2 is regarded as the main signaling cascade linked to the SDF-1 α -induced proliferation [169]. In addition, SDF-1 α mediates tube-like structure formation of endothelial cells also through the PI3K pathway [32]. In embryonic hippocampal neurons, SDF-1 α /CXCR4/G protein/ERK pathways stimulate production of glutamic acid decarboxylase-67 (GAD67) via Egr1 activation, which facilitates the maturation of GABAergic neurons [71].

SDF-1 α /CXCR4 Axis and cAMP

The cyclic AMP (cAMP) signaling is critical for SDF-1 α function in normal and malignant brain cells. Yang et al. [170] reported that SDF-1 α -induced tumor growth relies on persistent suppression of cAMP. Pharmacologic

elevation of cAMP inhibits growth of glioma cells in vitro and in vivo [170]. However, Odemis et al. [143] reported that dibutyryl cAMP enhances SDF-1 α -induced chemotaxis in astroglia. They thought that factors positively coupled to cAMP may augment CXCR4 production and promote SDF-1 α -induced chemotaxis [143].

Distribution of Tumor Cells with SDF-1 α Methylation

Epigenetic mechanisms participate in the regulation of the expression of SDF-1 α or CXCR4. One example is DNA methylation, a modification typically associated with inactivation of tumor suppressors. Methylation of SDF-1 α is detected in 34.2% (26/76) of astrocytomas by methylation-specific PCR in our study [19], mainly in low-grade astrocytomas, via DNA hypermethylation by DNMT1, -3A, and -3B. However, it is interesting to note that 61.8% of tumors, mainly high-grade astrocytomas, display elevated SDF-1 α mRNA, which suggests that SDF-1 α promoter hypermethylation is an early event in astrocytoma development [19]. In addition, the CXCR4 promoter methylation with decreasing mRNA and protein levels was found in pancreatic cancer [171]. But study on CXCR4 promoter methylation in gliomas has not been performed. Further, histone modifications are also involved in the regulation of the expression of SDF-1 α /CXCR4 in different cell types. Compared with brain microvascular pericytes, brain microvascular endothelial cells show an increase of histone H3 lysine 9 (H3K9) trimethylation and a decrease of H3K9 acetylation and H3K4 trimethylation [172].

Roles of the SDF-1 α /CXCR4 Axis in Glioma

SDF-1 α /CXCR4 Axis, Tumor Growth, and Cell Survival

SDF-1 α /CXCR4 is required for proliferation of glioma cells. Exogenous SDF-1 α induces proliferation of glioma cells in a dose-dependent manner [173]. SDF-1 α regulates growth of glioma through an autocrine/paracrine mechanism. The blockage of CXCR4 induces neurite outgrowth, cellular differentiation, and a significant increase of apoptosis [20, 174]. SDF-1 α /CXCR4-induced cellular proliferation is correlated with phosphorylation and activation of ERK 1/2 and Akt, as discussed above.

As for neural progenitor cells, SDF-1 α /CXCR4 mainly regulates not cell differentiation but cell motility, while overexpression of CXCR4 alone without SDF-1 α inhibits cell proliferation [175]. Moreover, overexpression of CXCR4 in the presence of bFGF conversely suppresses

cell proliferation, but further addition of SDF-1 α to the NPCs reverses the cell proliferation back to control levels [175]. In addition, Khan et al. [176] found that SDF-1 α supports survival and protects from apoptosis of postmitotic neurons through the counteraction of the Rb-E2F pathway. This finding suggests a neuronal protective role of the SDF-1 α /CXCR4 signal in physiological or neurodegenerative and neuroinflammatory conditions [176].

SDF-1 α /CXCR4 Axis and Tumor Migration

Migration is a hallmark of malignant gliomas and is the main reason for therapeutic failure and recurrence of the tumor [155]. The SDF-1 α /CXCR4 axis is of great importance for cell migration. Rosenkranz et al. [177] reported that transplanted human umbilical cord blood cells with positive CXCR4 invade into the hypoxic-ischemic lesion of the rat brain within only 1 day. SDF-1 α regulates the leading process of migration in glioma cells. Ehtesham et al. [178] found that invasive populations of glioma cells exhibited 25- to 89-fold higher expression of CXCR4 at the message and protein levels than noninvasive tumor cells did. In addition, neutralization of CXCR4 blocks the invasive ability of glioma cells [178]. SDF-1 α -mediated glioma migration requires a long-term stimulation of intermediate conductance Ca²⁺-activated K⁺ channel (IK(Ca)) activity via ERK1/2, but not PI3K [163].

SDF-1 α /CXCR4 Axis and Tumor Vasculogenesis/Angiogenesis

SDF-1 α and CXCR4 are expressed in both glioma and endothelial cells, which could represent a possible prognostic factor [21, 25, 28, 29]. The SDF-1 α /CXCR4 signaling plays an important role in glioma vasculogenesis and angiogenesis, which is regarded as a cross talk between endothelial and tumor cells. Vasculogenesis and angiogenesis, although endothelial cells are involved in both of them, are supposed to play distinct roles in the etiology of primary and recurrent malignant gliomas [179, 180]. Kenig et al. [181] reported that co-culturing of human GBM cells with HBMECs enhances tumor invasion and endothelial proliferation through the secretion of SDF-1 α and SDF-1 α -induced activity of MMP-9. Tumor vasculogenesis means homing and engraftment of bone marrow-derived vascular progenitors. SDF-1 α , not VEGF, recruits vascular progenitors to mitotic neovasculature [180, 182]. SDF-1 α also influences their differentiated phenotypes. Hypoxia interacts with tumor-secreted SDF-1 α to induce differentiation of vascular progenitor into pericytes and endothelium [182].

Imaging

Studies [22, 183] demonstrated patients with gliomas of CXCR4 overexpression showed a statistically significant increase in the intensity and extent of peritumoral T2-weighted magnetic resonance imaging (MRI) signal abnormalities. Given the importance of the SDF-1 α /CXCR4 signaling in the progress of glioma and poor prognosis of glioma, in the past years, a great deal of effort has been made to develop molecular imaging approaches to noninvasively evaluate SDF-1 α or CXCR4 status. Specific SDF-1 α or CXCR4 targeting imaging probes have been developed for multiple imaging modalities including single photon emission computed tomography (SPECT/CT). Nimmagadda et al. [184] radiolabeled anti-CXCR4 monoclonal antibodies (125)I-12G5, which were used in experimental brain tumor xenografts of mice. Immunoimaging of CXCR4 expression was obtained by SPECT/CT, with a specific accumulation of (125)I-12G5 in U87 tumors. The tumor-to-muscle uptake ratios reached 15 $\pm$ 3 at 48 h after injection [184]. Recombinant SDF-1 α was radiolabeled using 99mTc-S-acetylmercaptoacetyltriserine-N-hydroxysuccinimide ([99mTc-MAS3]-NHS) [185]. However, this 99mTc-labeled SDF-1 α radiotracer demonstrated no evidence of blood-brain barrier penetration.

SDF-1 α /CXCR4 Axis and Radio-/Chemoresistance in Glioma

Despite the high doses of radiation delivered in the treatment of patients with glioma, the tumors invariably recur within the irradiation field [180]. Tabatabai et al. [131] demonstrated that irradiation induces tumor satellite formation at 21 days after intracerebral implantation of glioma. Irradiation enhances the tropism of bone marrow-derived cells (BMDCs) and HPCs to the gliomas, the proliferation of HPCs, and the vasculogenesis of BMDCs [131, 180, 186]. During these processes, SDF-1 α has been identified as a key molecule. In glioma cells, SDF-1 α promoter is activated at 24 h after irradiation at 8 Gy [131]. SDF-1 α mediates the recruitment of HPCs to gliomas induced by irradiation via HIF-1 α and TGF- β [131, 187].

The SDF-1 α /CXCR4 axis is also correlated with chemotherapeutic sensitivity of gliomas. Combination of AMD3100 with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) synergistically inhibits the proliferation of GBM cells [188]. SDF-1 α was also identified as a predictor of the sensitivity of PDGF receptor inhibitor, named

imatinib/Glivec/Gleevec/STI571 in high-grade gliomas [189]. SDF-1 α can reverse the imatinib resistance of gliomas. These data suggest that molecule inhibitors of SDF-1 α /CXCR4 interactions, in combination with conventional radiotherapy or chemotherapy, are a promising combinatorial strategy.

Inhibition and Clinical Trials

Plerixafor (AMD3100) is a bicyclam molecular that selectively and reversibly antagonizes the binding of CXCR4 to its ligand, which is approved by FDA to aid, in combination with granulocyte-colony stimulating factor (G-CSF), in stem cell mobilization for the treatment of multiple myeloma or non-Hodgkin lymphoma. AMD3100 is also employed in the treatment of gliomas, especially GBM, through multiple mechanisms. Firstly, AMD3100 inhibits growth of intracranial glioblastoma by increasing apoptosis and decreasing the proliferation of tumor cells [167]. Secondly, AMD3100 impedes the subpopulations of stem cells in GBM to infiltrate to the protective hypoxic niche [190]. Thirdly, AMD3100 blocks the function of SDF-1 α , secreted by gliomas, by recruiting of NSCs to regions of brain tumor [43]. The combination between the antidepressant mirtazapine and the anti-fungal clotrimazole could block the intermediate conductance Ca²⁺-activated K⁺ channels, thereby inhibiting the SDF-1 α /CXCR4 signaling synergistically with AMD3100 [190]. AMD3465 is the second generation of the CXCR4 small inhibitor. Monomacrocyclic AMD3465 behaves like its predecessor in blocking antibody binding to CXCR4 and in vivo tumor growth, with 10-fold more effectiveness than AMD3100 [170, 191]. TC14012 is also developed as a peptidomimetic inverse agonist of CXCR4, recruiting β -arrestin to CXCR7 without detectable activation of G-proteins [192]. Cheng et al. [193] developed MABs 6H7 and 7D4, two specific monoclonal antibodies against human CXCR4. Interestingly, MAB 6H7 enhances SDF-1 α -induced proliferation in glioma cells, while MAB 7D4 blocks the function. Despite the difference in proliferation, both antibodies inhibit SDF-1 α -induced chemotaxis of glioma cells.

Oncolytic virotherapy holds promise as a novel cancer treatment platform for gliomas. However, many barriers exist in clinical trials, including immune inactivation, mislocalization, specific and nonspecific sequestration, and inadequate distribution [194]. NSCs are highly migratory and could selectively recruit to areas of brain tumors, which might be exploited as delivery vehicles for gene

therapy in gliomas [43, 195–197]. Tyler et al. [196] infected NSCs with a conditionally replicating adenovirus CRAd-Survivin(S)-pk7, thereby successfully migrating and delivering CRAd to glioma. Sonabend et al. [198] effectively infected human mesenchymal stem cells (hMSC) with CRAd as well as a chimeric 5/3 fiber or RGD backbone through CXCR4 promoter driving E1A. Both CRAd-CXCR4-5/3 and CRAd-CXCR4-RGD-loaded hMSC selectively migrated and released CRAds to glioma [196].

Clinical Implications and Future Challenges

Since AMD3100 (plerixafor) is already approved for clinical use, the use of AMD3100 is regarded as most promising for further investigations in human clinical trials as a proof of principle [199]. In glioblastoma patients, SDF-1 α /CXCR4 is responsible for restoring functional vasculature in irradiated tumors [199]. Furthermore, SDF-1 α increases when tumors escape from anti-VEGF therapy [200]. This has clinical implications for the use of CXCR4 antagonists in combination with other targeted agents [201] as well as conventional radiotherapy or chemotherapy drugs. However, a number of challenges remain, including the efficacy for glioma patients, the appropriate stage of glioma to treat, the possibility of penetrating the blood-brain barrier, and possible adverse events in combination with other therapies. It is worth noting that CXCR7, another receptor for SDF-1 α , is also essential for SDF-1 α -stimulated glioma progression [202]. So, there is a great market potential to develop anti-SDF-1 α monoclonal antibodies or antagonists that compete for both CXCR4 and CXCR7 receptors. Recently, Meincke et al. [203] synthesized fluorescent CXCL12-conjugates, which show a high sensitivity to detect primary and metastatic tumors by targeting tumor cells and tumor vasculature. However, this experiment showed no evidence of blood-brain barrier penetration. There is still a long way to go to find SDF-1 α - or CXCR4-targeting imaging probes with high sensitivity and specificity for brain tumors.

Discussion

Increasing evidence supports that the SDF-1 α /CXCR4 signaling plays a vital role in an enormous diversity of processes in both brain development and glioma progression, including migration, distribution, differentiation, proliferation, vasculogenesis/angiogenesis, and cellular

functions. Gliomas are highly invasive and resistant to radiation and chemotherapy, and aberrant SDF-1 α /CXCR4 signaling contributes to this resistance. Thus, the SDF-1 α /CXCR4 signaling remains an attractive target for therapeutic intervention in glioma. However, a number of important questions remain unanswered. Firstly, how to press the switch of SDF-1 α changing the SDF-1 α /CXCR4 signaling from the endocrine loop to the autocrine and/or local paracrine loop in brain development and glioma progression. As CXCR4 is constitutively expressed in differentiated normal or tumor tissues, it is much more important to define possible mechanisms underlying the regulation of chemokine SDF-1 α . Secondly, CXCR4 exhibits the highest mRNA levels at an early stage of brain development. CXCR4 expression tapers off soon during brain development. Another question that deserves further study is the controlling system or the upstream signal transduction of CXCR4 silence during brain development. Because many expressional and functional features of SDF-1 α /CXCR4 signaling appear to be shared by brain development and glioma progression, studies in the field of brain development may provide valuable tactics for glioma treatment.

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Disclosure Statement

There are no financial or commercial conflicts of interest involved in this study.

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