Multiple roles of chemokine CXCL12 in the central nervous system: A migration from immunology to neurobiology

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Abstract

Chemotactic cytokines (chemokines) have been traditionally defined as small (10–14 kDa) secreted leukocyte chemoattractants. However, chemokines and their cognate receptors are constitutively expressed in the central nervous system (CNS) where immune activities are under stringent control. Why and how the CNS uses the chemokine system to carry out its complex physiological functions has intrigued neurobiologists. Here, we focus on chemokine CXCL12 and its receptor CXCR4 that have been widely characterized in peripheral tissues and delineate their main functions in the CNS. Extensive evidence supports CXCL12 as a key regulator for early development of the CNS. CXCR4 signaling is required for the migration of neuronal precursors, axon guidance/pathfinding and maintenance of neural progenitor cells (NPCs). In the mature CNS, CXCL12 modulates neurotransmission, neurotoxicity and neuroglial interactions. Thus, chemokines represent an inherent system that helps establish and maintain CNS homeostasis. In addition, growing evidence implicates altered expression of CXCL12 and CXCR4 in the pathogenesis of CNS disorders such as HIV-associated encephalopathy, brain tumor, stroke and multiple sclerosis (MS), making them the plausible targets for future pharmacological intervention.

Keywords

CXCL12; CXCR4; Chemokines; Chemokine receptors; CNS development; Neuromodulation; CNS disorders

1. Introduction

Chemokines are small, mostly secreted proteins that were initially implicated in the regulation of leukocyte trafficking during host defense and pathological immune responses. Chemokines can be classified into CXC, CC, C or CX3C subfamilies based on the arrangement of the two cysteine residues near the N-terminus (Zlotnik A and Yoshie O, 2000). Chemokine receptors are G protein-coupled receptors (GPCRs) with seven-transmembrane domains that are highly conserved in evolution (Fredriksson R et al, 2003; Kawasawa Y et al, 2003; DeVries ME et al, 2006). By binding to their cognate receptors, chemokines activate a series of downstream signaling pathways to guide the movement of leukocytes to target tissues or organs (Rot A and von Andrian UH, 2004). Directional movement of leukocytes through a concentration gradient of chemokine is defined as "chemotaxis". So far, 53 human chemokines and 23 chemokine receptors have been cloned or characterized (http://cytokine.medic.kumamoto-u.ac.jp/). Under

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a new systematic nomenclature the chemokines are named according to subfamilies (such as CC or CXC), along with letter "L" to indicated "ligand" and a number that corresponds to the order of cloning and characterization. Thus, SDF1 is now termed CXCL12 and the receptor nomenclature follows this family assignment. CXC receptors respond to CXC chemokines (for the most part). To gain receptor designations, a GPCR must bind chemokines with high affinity and specificity and must signal (mobilize Ca^{2+}, for example).

As an important member of the CXC subfamily, CXCL12 has been widely explored in the hematopoietic system. In 1993, a CXCL12 cDNA clone was first isolated from a murine bone-marrow stroma cell line by the signal sequence trap method and the gene was originally named SDF1 (stromal cell-derived factor 1) (Tashiro K et al, 1993). Several years later, two groups simultaneously and independently identified its receptor, an orphan GPCR called LESTR/fusin (Bleul CC et al, 1996a; Oberlin E et al, 1996). LESTR/fusin was also the first identified coreceptor for human immunodeficiency virus (HIV-1) infection of CD4+ lymphocytes (Feng Y et al, 1996) and administration of CXCL12 inhibited infection by T-tropic HIV-1 of HeLa-CD4 cells (Bleul CC et al, 1996a; Oberlin E et al, 1996). According to its ability to bind and respond to CXCL12, the designation CXCR4 was adopted to replace LESTR/fusion.

CXCL12/CXCR4 plays pleiotropic functions in the peripheral immune system. CXCL12 is a highly efficacious chemoattractant for lymphocytes and monocytes but not neutrophils (Bleul CC et al, 1996b). CXCL12/CXCR4 not only regulates the development of T and B lymphocytes but also contributes to the survival of mature lymphocytes and in the generation of memory T cells (Klein RS and Rubin JB, 2004). Recent studies indicate that CXCL12/CXCR4 enhances the inflammatory infiltration of neutrophils or lymphocytes in diverse models and settings involving acute inflammation or fulminant infection (Wald O et al, 2004; Ding Z et al, 2006; Petty JM et al, 2007). CXCL12 is an important regulator for homing of hematopoietic progenitor cells (HPCs) to the bone marrow (BM) microenvironment (Lapidot T et al, 2005). Deficient development of blood cells and heart were also described in CXCL12 knockout (KO) mice (Nagasawa T et al, 1996). Interestingly, similar phenotypes were observed in CXCR4 KO mice too (Tachibana K et al, 1998; Zou YR et al, 1998), suggesting that the interaction between CXCL12 and CXCR4 may be one- to one- relationship. Recent results from studying an alternative non-signaling CXCL12 receptor, termed CXCR7 (Burns JM et al, 2006), suggest that the CXCL12/CXCR4 relationship is not entirely exclusive.

CXCL12/CXCR4 is involved in the embryonic development of diverse peripheral tissues such as blood vessels, muscle, primordial germ cell (PGC) and sensory lateral line etc (Nagasawa T et al, 1996; Tachibana K et al, 1998; Zhu YR et al, 1998; David NB et al, 2002; Odemis V et al, 2005; Sapede D, 2005; Haas P and Gilmour D 2006). In addition, CXCL12/CXCR4 participates in peripheral pathogenetic processes. For instance, CXCL12/CXCR4 may in part regulate T cell accumulation in rheumatoid synovial tissues (Buckley CD et al, 2000; Nanki T et al, 2000). CXCR4 is the most widely expressed chemokine receptor in many different cancers and the effects of CXCL12 on CXCR4-bearing tumor cells include a wide diversity of functions (growth, differentiation) besides migration (Zlotnik A, 2006). CXCL12 stimulates survival and growth of neoplastic cells in a paracrine fashion, which can be further enhanced by CXCL12-induced angiogenesis (Burger JA and Kipps TJ, 2006).

The central nervous system (CNS) is an immunologically specialized site where entry of immune cells is tightly regulated. Immune responses are not initiated in the CNS due to the absence of endogenous antigen-presenting cells (Ransohoff RM et al, 2003). Both CXCL12 and CXCR4 are constitutively expressed in the CNS (Tham TN et al, 2001; Banisadr G et al, 2003; Tissir F et al, 2004), but do not mediate leukocyte recruitment to that organ under physiological conditions. Although deficient CNS development has been reported in either CXCL12 or CXCR4 KO mice (Zou YR et al, 1998, Lu M et al, 2002; Lieberam I et al,

2005), the detailed roles of CXCL12/CXCR4 in the adult CNS remain under active investigation. In this review, we will discuss several established functions of CXCL12/CXCR4 in the CNS.

2. CXCL12/CXCR4 signaling pathways

Similar to other chemokines, CXCL12 binds its receptor CXCR4 to activate a series of down-stream signaling pathways (Fig. 1). The interaction between CXCL12 and CXCR4 can be blocked by a bicyclam antagonist AMD31000 (Schols D et al, 1997). Initial binding of CXCL12 to the extracellular components of CXCR4 modifies the tertiary structure of the receptor, allowing the intracellular part to activate heterotrimeric G-proteins (Rot A and von Andrian UH, 2004). Signaling pathways triggered by CXCL12 are mediated both by pertussis toxin (PTX)-sensitive $G\alpha i$ and by Gq components. Activated heterotrimer G proteins exchange guanosine diphosphate (GDP) for guanosine triphosphate (GTP) and dissociate into α- and $\beta\gamma$-subunits respectively (al-Aoukaty A et al, 1996;Kuang Y et al, 1996). The a subunit further activates phospholipase C (PLC), causing the generation of diacylglycerol (DAG) and inositol 1, 4, 5 trisphosphate (IP_3). IP_3 binds its specific receptor in the endoplasmic reticulum and releases Ca^{2+} from intracellular stores. Transient Ca^{2+} elevation is an important consequence of ligand-induced chemokine receptor activation (Boutet A et al, 2001;Gillard SE et al, 2002). Binding of CXCL12 to CXCR4 also induces the activation of phosphoinositide-3 kinase (PI3K) that activates downstream AKT, PyK2 and nuclear transcriptional factor $NF_\kappa B$ signaling pathways (Bajetto A et al, 2001;Han Y et al, 2001a;Fernandis AZ et al, 2004;Lee BC et al, 2004;Alvarez S et al, 2005;Kukreja P et al, 2005;Florio T et al, 2006). G-protein dependent activation of CXCR4 also induces several MAPKs signaling pathways such as ERK, JNK and P38 (Bajetto A et al, 2001;Han Y et al, 2001a;Han Y et al, 2001b;Fernandis AZ et al, 2004;Alvarez S et al, 2005). In addition, CXCL12/CXCR4 activates the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway in a PTX independent manner (Vila-Coro AJ et al, 1999;Soriano SF et al, 2003;Soldevila G et al, 2004).

CXCL12/CXCR4 signaling is regulated by G protein-coupled receptor kinases (GRKs) and β-arrestins (Fig. 1). CXCL12 activation of CXCR4 desensitizes CXCR4 though GRK-mediated receptor phosphorylation and β-arrestin binding (Cheng ZJ et al, 2000;Fong AM et al, 2002;Vroon A, 2004). β-Arrestin2 enhances CXCR4-mediated activation of p38 MAPK that is critically involved in CXCR4-mediated chemotaxis (Sun Y, et al, 2002).

3. Expression of CXCL12 and CXCR4 in the CNS

Both CXCL12 and CXCR4 are constitutively expressed in the developing and mature CNS. In early developmental stages, expression of CXCR4 is mainly detected in the ventricular zone (VZ), subventricular zone (SVZ) and marginal zone (MZ), which are specialized niches for precursors to survive and proliferate. In the mature CNS, CXCL12 or CXCR4 is detected in a remarkable diversity of differentiated cells. In some cases, expression of CXCL12 complements that of CXCR4 and abnormal elevation of both CXCL12 and CXCR4 has been a prominent feature in varied pathological states.

3.1 Constitutive expression

In the developing mouse CNS, expression of CXCR4 starts as early as embryonic day 8.5 (E8.5) and is sustained until adulthood (McGrath KE et al, 1999; Tissir F et al, 2004; Lieberam I et al, 2005). CXCR4 expression is mainly detected in the ventral part of the neural tube during early neural development. However, CXCL12 expression can be found in mesenchymal cells. Beginning from E15.5, both CXCL12 and CXCR4 are expressed in the cortex, olfactory bulb, hippocampus and cerebellum as well as the meninges and endothelia. CXCR4 immunoreactivity has been reported in virtually all CNS cells: neurons, astrocytes, microglia,

oligodendrocytes and endothelial cells (Lavi E et al, 1997; Jazin EE et al, 1997; Bajetto A et al, 1999; McGrath KE et al, 1999; van der Meer P et al, 2000; Tham TN et al, 2001; Banisadr G et al, 2002; Banisadr G et al, 2003; Krumbholz M et al, 2006), although some observations have not been validated by multiple consistent findings.

3.2. Complementary expression of CXCL12 and CXCR4

In developing and mature CNS, there is a complementary expression pattern for CXCL12 and CXCR4 that is consistent with their roles in mediating migration, proliferation and survival (Fig. 2). In mouse cerebellum after birth, expression of CXCR4 is observed in the granule cell precursors in the external granular layer (EGL) while expression of CXCL12 is detected in the pial surface adjacent to the EGL (Ma Q et al, 1998;Zou YR et al, 1998;Reiss K et al, 2002). In dentate gyrus (DG) and cortex, expression of CXCR4 is detected in the migrating neuronal precursor cells in the cortical primordium and MZ, while CXCL12 is expressed in the associated pia matter (Bagri A et al, 2002;Lu M et al, 2002).

3.3. Inducible expression

Although CXCL12 is constitutively expressed in the adult CNS, its expression is normally controlled at a relatively low level. CXCL12 can be briefly up-regulated under some pathathological situations such as HIV 1-asociated dementia, brain tumor, ischemia (stroke) and Neuroinflammation (Rempel SA et al, 2000; Rostasy K et al, 2003; Hill WD et al, 2004; Metelitsa LS et al, 2004; Miller JT et al, 2005; Peng H et al, 2006; Tabatabai G et al, 2006). Astrocytes and vascular endothelial cells in the parenchyma have been suggested as two primary cell sources for inducible CXCL12. In ischemia, the local hypoxic microenvironment activates transcription factor hypoxia-inducible factor-1 (HIF-1) that regulates CXCL12 gene expression in endothelial cells, resulting in selective expression of CXCL12 in ischemic tissue in direct proportion to reduced oxygen tension (Ceradini DJ et al, 2004). In acquired immunodeficiency syndrome (AIDS) patients, quinolinic acid (QUIN) is an important neurotoxin associated with AIDS dementia complex (ADC) and mainly released from mononuclear phagocytes (which may be infected by HIV-1 or stimulated in paracrine fashion by cytokines released from infected cells). QUIN up-regulates the expression of CXCL12 and CXCR4 in astrocytes (Croitoru-Lamoury J et al, 2003a; Guillemin GJ et al, 2003). In multiple sclerosis (MS), CXCL12 protein is elevated and detected on astrocytes and blood vessels (Ambrosini E et al, 2005; Krumbholz M et al, 2006). In tumors, expression of both CXCL12 and CXCR4 increases with increasing tumor grade and over expression of CXCR4 was observed in the neovascular endothelial cells (Rempel SA et al, 2000).

Up-regulation of either CXCL12 or CXCR4 relies on other regulators. HIF-1 and VEGF enhance the expression of CXCR4 in glioblastoma (Zagzag D et al, 2006). IL-1β induces CXCL12 in astrocytes by ERK and PI3K signaling pathways (Calderon TM et al, 2006; Peng H et al, 2006). Our lab demonstrated that CXCR4 expression by primary mouse astrocytes is suppressed by exposure to TNF-α (Han Y et al, 2001a). In contrast, other labs found that TNF-α up-regulates the expression of CXCR4 (Croitoru-Lamoury J et al, 2003b), suggesting cytokine-dependent CXCR4 regulation is a complicated process.

4. Roles of CXCL12/CXCR4 in the development of CNS

4.1 Migration of Neuronal progenitor Cells

Brain cortex exhibits a highly laminar organization arising during early development when newborn neurons migrate from proliferative VZ and spread into other cortical layers. There are two basic migration patterns: short range radial migration, in which neurons use the radial glial scaffold to migrate to their final destination; and long range tangential migration dependent on substrates other than radial glial cells (Marin O and Rubenstein JL, 2003).

CXCL12/CXCR4 directly regulates the migration of cortical neuronal precursors, including cortical Cajal-Retzius cells (CR), cerebellar granule precursor cells (GPC) and dentate gyrus GPC, a function which is essential for the formation of complex laminated cortex structures during early development (Fig. 2).

4.1.1. Cortical Cajal-Retzius (CR) cells—In the developing brain cortex, Cajal-Retzius (CR) cells are a transient population of neurons located in the marginal zone (MZ), directly adjacent to the meninges (Derer P and Derer M, 1990; Marin-Padilla M, 1990; Del Rio JA et al, 1995; Verney C and Derer P, 1995). The major function of CR cells is to regulate cortical lamination by secreting the glycoprotein reelin, which maintains the radial glial scaffold that governs the migration of granule cells (D'Arcangelo G et al, 1995; Ogawa M et al, 1995; Super H et al, 2000). Recent studies suggest three major CR cell sources in the embryonic telencephalon, including the cortical hem, the septum and the ventral pallium (Takiguchi-Hayashi K et al, 2004; Bielle F et al, 2005; Yoshida M et al, 2006). CR cells initially radially spread from VZ to MZ and subsequently migrate long distances tangentially along the cortical surface (Takiguchi-Hayashi K et al, 2004; Bielle F et al, 2005; Muzio L and Mallamaci A, 2005; Yoshida M et al, 2006).

Expression of CXCR4 is detected in the MZ CR cells from preplate (E13.5) to early postnatal stage (P3) of neocortical development (Stumm RK et al, 2003; Borrell V and Marin O, 2006) while expression of CXCL12 is detected in the meninges (Stumm RK et al, 2003; Borrell V and Marin O, 2006). In either CXCL12−/− or CXCR4−/− mice, there is obvious ectopic dispersion of CR cells that are displaced into deeper cortical layers (Stumm RK et al, 2003; Paredes MF et al, 2006), which suggests that CXCL12/CXCR4 may influence the early localization of CR cells. Recently, Borrel and coworkers (2006) demonstrated that meninges themselves are the important substrate for CR cell tangential migration. They performed a series of transplant assays by which green fluorescent protein (GFP) positive cortical hem tissues were transplanted into wild type brain slices. After 48 hours, they observed the consistent CR cell tangential migration in association with the intact meninges rather than the cortical neuroepithelium (Borrell V and Marin O, 2006). Further, they demonstrated both in vivo and in vitro that CXCL12 triggers the migration of CR cells by binding CXCR4.

Paredes et al (2006) demonstrated similar roles of CXCL12 in the development of CR cells by studying methylazoxymethanol (MAM) treated rats. MAM is a DNA-alkylating agent that causes the accumulation of defects during DNA replication of dividing cells (Kisby GE et al, 1999). They observed disruption of the MZ in the E15 embryos of MAM treated Sprague Dawley (SD) rats, with the MZ becoming thicker. Further, many reelin-positive CR cells redistributed to the deeper cortical layers, a similar phenotype to that observed in CXCL12−/− and CXCR4−/− mice (Stumm RK et al, 2003; Paredes MF et al, 2006). However, MAM treating does not directly cause the abnormal distribution of CR cells, which occupy the MZ before drug administration at E15. Furthermore, exogenous CXCL12 rescued the developmental defects caused by MAM, suggesting that loss of CXCL12 might lead to the defective migration of CR cells. Additional studies showed that MAM causes meningeal injury and defects in the meningeal basement membrane leads to the loss of CXCL12 expression by leptomeninges. Therefore, CXCL12/CXCR4 directly regulates the tangential migration of CR cells and contributes to the formation of laminated cortex. In addition, CXCL12 is expressed in the subventricular zone/intermediate zone (SVZ/IZ) and CXCL12 secreted from the proliferating precursors of projection neurons has been suggested to regulate the invasion of interneurons during corticogenesis (Tiveron MC et al, 2006).

4.1.2. Cerebellar granule precursor cells—In the developing cerebellum, there is a subpial proliferative zone called external granular layer (EGL), occupied by granule cell precursors and other glial progenitor cells after their generation from the VZ of the rhombic

lip (Jensen KF and Altman J, 1982; Hausmann B and Sievers J, 1985). Starting from E10, granule cell precursors migrate tangentially to cover most of the cerebellar surface at E15, following a lateromedial and posteroanterior trajectory (Sotelo C, 2004). After transient proliferation in the EGL, granule cell precursors exit the cell cycle and become postmitotic granule cells. Postmitotic granule cells migrate radially inward to form the internal granule layer (IGL) at the later stages (Altman J and Bayer SA, 1985).

Expression of CXCR4 had been implicated in the developing EGL (Zou YR et al, 1998; Tissir F et al, 2004) and CXCR4 protein can be found in cultured granule progenitor cells in vitro (Klein RS et al, 2001; Reiss K et al, 2002). In complementary fashion, CXCL12 is expressed in the meninges (Tham TN et al, 2001; Klein RS et al, 2001; Zhu YR, 2002; Reiss K et al, 2002). Zou et al (1998) first reported the abnormal migration of granule cell precursors in the cerebellar anlage of CXCR4−/− mice during first postnatal week. They found ectopic clusters of dividing granule cells, beneath the Purkinje cell layer or intermingled with Purkinje cells. Similar abnormal phenotypes were observed in the CXCL12−/− cerebellum (Ma Q et al, 1998).

A widely accepted hypothesis for explaining these phenotypes in the CXCR12−/− and CXCR4 −/− mice is that CXCL12 prevents granular cell precursors from prematurely exiting the EGL (Zou YR et al, 1998). In vitro, CXCL12 was found to be a chemotactic factor for cells isolated from EGL (Klein RS et al, 2001) and CXCL12-induced chemotaxis was negatively regulated by an EphB receptor whose ligation activates a PDZ-RGS3 protein (Lu Q et al, 2001). Within EGL, Reiss et al (2002) demonstrated that CXCL12 binds to and is concentrated by heparan sulfate proteoglycans (HSPG), using a similar mechanism to that employed in the CXCL12-mediated adhesion of leukocytes to the endothelial surface. In addition, CXCL12 may also enhance the proliferation of granule cell precursors mediated by Sonic hedgehog (SHH) through the activation of down-stream signaling pathways that eventually lead to increased intracellular cAMP (Klein RS et al, 2001). Therefore, CXCL12 has two basic functions in cerebellogenesis: one is to attract and maintain the granule cell precursors within the EGL; a second function is to promote granule cell precursor proliferation. Besides ephrin B signaling, there are many other signaling pathways such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neuregulin (NRG), astrotactin and tenascin, tissue plasminogen activator, platelet-activating factor (PAF), cyclin-dependent kinase 5(Cdk-5), 9-O-acetyl GD3 and somatostatin that have been suggested in the regulation of cerebellar granule cell migration (Komuro H and Yacubova E, 2003). However, the detailed relationships between these components and CXCL12/CXCR4 have not been addressed.

Another possible mechanism to explain the abnormal distribution of granule cell precursors in either CXCL12−/− or CXCR4−/− mice is that CXCL12 may directly guide the tangential migration of granule cell precursors in the EGL along the cerebellar surface during early gestation. In support of this possibility, CXCR4 is expressed in the germinal region of the rhombic lip, the only region from which the cerebellar granule cell precursors are generated (Wingate RJ and Hatten ME, 1999; Tissir F et al, 2004). Previous studies demonstrated that selective destruction of the meninges in this region causes reduction of the superficial basal lamina, a misrouting of cell migration within the VZ and the abnormal development of radial glia (Hartmann D et al, 1992; Sievers J et al, 1994; Hartmann et al, 1998).

4.1.3 Dentate gyrus (DG) granule precursor cells—The early development of dentate granule cells initiates with radial migration of cells from the dentate neuroepithelium to the dentate gyrus anlage. The migrating stream contains both precursor cells and postmitotic neurons that determine the morphogenesis of the primary dentate gyrus and hillus. As development proceeds, most precursor cells in the hillus exit the cell cycle to become postmitotic granule cells. Only a small proportion of granule cell precursors remain within the

subgranular zone (SGZ), a thin border between the dentate GCL and hillus (Pleasure, SJ et al, 2000). Dentate GCL represents an important site of adult neurogenesis. During development, dentate CR cells migrate within the MZ from the supra-granular blade, where they can be observed from perinatal stages onward, toward the developing infra-granular blade (Super H et al, 1998). Dentate CR cells influence the migration of granule cells in the dentate gyrus by acting on the radial glial scaffold (Frotscher M et al, 2003).

In early developing DG, CXCL12 is constitutively expressed in the meninges overlying the hippocampus and in the hippocampal primordium itself near the hippocampal fissure, overlying the developing DG (Bagri A et al, 2002; Lu M et al, 2002). During the first postnatal weeks, expression of CXCL12 is detected in meninges, CR cells and maturing DG granule cells (Berger O et al, 2007). In adulthood, expression of CXCL12 is detected in the blades of DG and some cells in the hillus (Lu M et al, 2002). In CXCR4−/− mice, ectopic dispersion and abnormal migration of granule cells were observed. Abnormal development of the DG in CXCR4−/− mice was potentially caused by deficient migration of granule cells since over-expression of CXCL12 in vitro disrupted the migration of granule cells (Bagri A et al, 2002; Lu M et al, 2002).

4.1.4. Others—CXCL12/CXCR4 has also been suggested in the development of other tissues or organs such as peripheral nervous systems (PNS), gonadotropin-releasing hormone (GnRH) neurons, primordial germ cells (PGCs), lateral line, facial motor neurons and muscle. Recent studies demonstrated that CXCL12 regulates the migration of sensory neuron precursors in the dorsal root ganglia (DRG) (Belmadani A et al, 2005). CXCR4 null mice exhibited small and malformed DRGs and CXCL12 acted as a chemoattractant for the cells from neural tube explants (Belmadani A et al, 2005). Similarly, Knaut et al (2005) reported that trigeminal sensory ganglia (TgSG) neurons were ectopically located in the CXC4b morphant zebrafish embryos (embryos injected with morpholine-conjugated antisense oligonucleotides) while both the number of TgSG neurons and axon projections were normal. In CXCR4−/− mice, most GnRH neurons also failed to exit the vomeronasal organ (VNO) at E13, and comparatively few GnRH neurons reached the forebrain (Schwarting GA et al, 2006). Primordial germ cells (PGCs) are the founders of sperm or oocytes. In zebrafish, knocking down CXCL12 or receptor CXCR4 results in severe defects in PGC migration (Doitsidou M et al, 2002). Inhibition of PI3K signaling in PGCs slows down their migration and leads to abnormal PGC morphology as well as to reduced stability of filopodia (Dumstrei K et al, 2004). PGCs undergo directed migration through tissues of embryos in CXCL12−/− mice, but the numbers of PGCs in the gonads are significantly reduced without evident effects on the proliferation of PGCs (Ara T et al, 2003).

The posterior lateral line (PLL) is a mechanosensory system located caudally in fish and amphibians. Recent studies demonstrated that inactivation of CXCL12 and CXCR4 prevents PLL primordium migration, resulting in the formation of defective PLL (David NB et al, 2002; Li Q et al, 2004; Haas P and Gilmour D, 2006). The migration of motor neurons of the facial nucleus from rhombomere 4 to 6 was also affected in CXCL12 morphants (Sapede D et al, 2005). In CXCR4 mutant mice, the number of muscle progenitors that colonized the anlage of the tongue and the dorsal limb was reduced. Changes in the distribution of the muscle progenitor cells were accompanied by increased apoptosis, indicating that CXCR4 signals provide not only attractive cues but also control survival possibly through interacting with Gab1, an adaptor protein that transduces signals elicited by tyrosine kinase receptors (Vasyutina E et al, 2005).

4.2. Axon guidance and pathfinding

The development of the CNS depends not only on the well-regulated migration of precursor cells but also the establishment of complete circuitry by extending neuritic processes (axons and dendrites) to target neurons to form synaptic connections. Axonal growth cones are guided by axonal guidance cues (Tessier-Lavigne and Goodman, 1996). CXCL12 serves as a guidance cue to regulate axon projection, interacting with other axon guidance cues.

Wu et al (2001) first reported that slit-2, a secreted protein previously known as a mediator of repulsion in axon guidance and neuronal migration, also inhibits leukocyte chemotaxis induced by CXCL12. The inhibitory effects of slit-2 could be reconstituted by CXCR4 and slit receptor Roundabout (Robo). This crosstalk between CXCL12 and slit-2 in leukocytes raised the question whether chemokines play a role in axon guidance. This line of research showed that CXCL12 mediates several important axon guidance cues and also directs relative axon repulsion. For instance, CXCL12 reduces the repellent activities of slit-2 on cultured retinal ganglion cell axons, of semaphorin 3A on dorsal root ganglion sensory axons, and of semaphorin 3C on sympathetic axons (Chalasani SH et al, 2003). In zebrafish, antisense knockdown of CXCL12 or CXCR4 induced retinal axons to follow aberrant pathways within the retina. Further, retinal axons deviated from their normal pathways and extended to cells ectopically expressing CXCL12 within the retina (Li Q et al, 2005). However, these effects may be indirect since CXCL12 does not have detectable attractive or repellent effects on retinal or DRG axons by itself (Chalasani SH et al, 2003). In cultured retinal axons, CXCL12 mediates reduced responsiveness to slit-2 (Chalasani SH et al, 2007). In vivo, reducing CXCL12 signaling rescues retinal axon pathfinding errors in zebrafish morphants that have a partial functional loss of robo as compared with morphants that completely lack robo (Chalasani SH et al, 2007), indicating that guidance or repulsive effects of CXCL12 relies on other axon guidance cues. However, the detailed molecular mechanism is not well known.

Chalasani (2003) has suggested that modulation of intracellular cyclic nucleotides may influence the guidance effects of CXCL12 towards axons. In slit-2 induced growth cone collapse experiments, either PTX or CXCR4 antagonist AMD3100 could block the effects of CXCL12. cAMP antagonist RpcAMPS also abrogated the modulation mediated by CXCL12. RpcAMPS failed to affect slit-2-induced collapse. Together, the results indicated that binding of CXCL12 to CXCR4 elevates intracellular cAMP level and modulates axonal projection. Rho-GTPase associated with CXCL12 signaling has also been implicated in axon outgrowth (Arakawa Y et al, 2003). In zebrafish, CXCL12 activates two distinct Rho-dependent pathways with opposite consequences. At low concentrations, CXCL12 stimulates a Rho-dependent pathway that facilitates axon elongation. In contrast, Rho/ROCK activation stimulated by a higher concentration of CXCL12 repressed axon formation and induced arrest in axon length (Arakawa Y et al, 2003).

Lieberam et al (2005) demonstrated that CXCL12/CXCR4 is required for the ventral trajectory of mouse spinal motor neurons (vMN). Briefly, there are two types of motor neurons (ventral motor neurons-vMNs and dorsal motor neurons-dMNs), choosing different pathways to project axons to peripheral muscle (Gutherie S and Lumsden A, 1992). Expression of CXCR4 was only detected in the axonal growth cones of vMN but not dMN. Interestingly, many CXCR4 −/− vMN axons adopted a dMN-like trajectory despite preservation of their vMN transcriptional identity and initial axon projection (Lieberam I et al, 2005).

In zebrafish, peripheral sensory efferent projection requires intact CXCL12/CXCR4 signaling (Gilmour D et al, 2004; Sapede D et al, 2005). The peripheral PLL in zebrafish receives axonal afferent inputs from two different efferent nuclei in the hindbrain (Metcalfe WK et al, 1985). Although migration of PLL was inhibited in CXCL12 or CXCR4 morphants, the sensory axons remained associated to the primordium, which suggests efferent projection and migration of

PLL are two independent phenomena (David NB et al, 2002). By generating a series of genetic mosaic embryos from zebrafish, Gilmouir D et al (2004) demonstrated that PLL, a migrating cell cluster, provides similar cues that are sufficient to steer its associated nerve throughout the entire extension process.

Burns et al (2006) identified an orphan GPCR, RDC1 as a second receptor for CXCL12, designated CXCR7. To date, limited evidence is available regarding the functional roles of CXCR7. In particular, knockdown studies in zebrafish suggest that CXCR7 is active during vasculogenesis. In CXCR7 morphant zebrafish, abnormal distribution of neuromasts were oberserved, suggesting CXCR7 is required for guidance of primordium migration (Dambly-Chaudiere C et al, 2007). However, the underlying mechanism remains to be further addressed.

5. Roles of CXCL12/CXCR4 in neural progenitor cells (NPCs)

NPCs or neural stem cells are self-renewing multi-potential cells that give rise to residual neurons, astrocytes and oligodendrocytes in embryonic and mature CNS (Gage FH et al, 1995; Brustle, O et al, 1997). It has been suggested recently that NPCs are associated with embryonic/adult neurogenesis and tissue repair. In mature CNS, SVZ/olfactory bulb system and dentate gyrus SGZ has been suggested as the two major neurogenic regions that host NPCs constitutively for adult neurogenesis. Thored P et al (2006) demonstrated that endogenous NPCs continuously supply the injured adult brain with new neurons, which suggests novel self-repair strategies to improve recovery after stroke. The expression pattern of CXCR4 in the neurogenic regions of postnatal brain is consistent with the distribution of NPCs (Tran PB et al, 2007). In vitro, expression of CXCR4 has been widely reported in cultured NPCs isolated from different regions of adult brain (Ji JF et al, 2004; Peng H et al, 2004; Tran, PB et al, 2004; Dziembowska M et al, 2005; Tran PB et al, 2005). Interestingly, important functions of CXCL12/CXCR4 have been demonstrated in hematopoietic progenitors, including homing to the bone marrow; trafficking in the circulation; survival; and proliferation (Lataillade JJ et al, 2004). It is worth noting that similar roles for CXCL12/CXCR4 have been suggested for adult NPCs.

First, CXCL12/CXCR4 regulates the migration of adult NPCs. In vitro, administration of CXCL12 directly induces adult NPC chemotaxis (Reiss K et al, 2002; Imitola J et al, 2004; Peng H et al, 2004). Imitola et al (2004) demonstrated that human NPCs migrate in vivo (including from the contralateral hemisphere) toward an infarcted area, where local astrocytes and endothelium up-regulate CXCL12. Robin et al (2006) found that cultured NPCs harvested from the normal adult SVZ, when they were overlaid onto stroke brain slices, exhibited significantly increased migration. Blocking CXCL12 by a neutralizing antibody against CXCR4 significantly attenuated stroke-enhanced NPC migration. Several signaling pathways may mediate CXCL12 induced NPC migration, including IP3; extracellular signal-regulated kinases1/2; AKT, c-Jun N-terminal kinase; intracellular Ca^{2+} and reduction of cAMP (Peng H et al, 2004). Second, CXCL12 stimulates the proliferation of adult NPCs (Tran PB et al, 2004; Dziembowska M et al, 2005; Tran PB et al, 2005). Exposure of CXCL12 to quiescent NPCs enhances proliferation, promotes chain migration and transmigration (Imitola J et al, 2004). CXCL12 enhances the proliferation of NPCs in vitro, dependent on the ERK1/2 and PI-3 kinase pathways (Gong X et al, 2006). CXCL12 may promote survival, but also maintains NPCs in a quiescent state (Krathwohl MD and Kaiser JL, 2004).

6. Roles of CXCL12/CXCR4 in the adult CNS

6.1. Neuromodulation

Constitutive expression of CXCR4 in mature neurons suggested that CXCL12/CXCR4 might modulate neurotransmission. Limatola C et al (2000) first reported that Purkinje neurons in

cerebellar slices responded to CXCL12 application by a slow inward current followed by an increase of both intracellular Ca^{2+} and spontaneous synaptic activity. The same group reported that the amplitude of evoked excitatory postsynaptic currents (EPSC) of Purkinje neurons was reversibly reduced by CXCL12 application (Ragozzino D et al, 2002). They suggested that neuromodulatory effects of CXCL12 were indirect, caused by glutamate release from glial cells. Recent studies found that CXCL12 controls melanin-concentrating hormone neuron excitability not only through indirect glutamate/GABA release but also through direct G protein activated K+ channel (GIRK) current activation (Guyon A et al, 2005; Guyon A et al, 2006). By blocking CXCR4, antagonist human Immunodeficiency virus (HIV)-1 gp120 inhibits the long-term potentiation (LTP) in the CA1 region of rat hippocampus through indirect release of gamma-aminobutyric acid type A (GABAA) while no effects were observed on basal synaptic transmission (Dong J and Xiong H, 2006). CXCL12 affects the electrical activity of arginine vasopressin (AVP) neurons, resulting in changes in AVP release (Callewaere C et al, 2006). Chemokines and gp120 have been suggested to facilitate pain pathways via direct actions on chemokine receptors expressed by nociceptive neurons (Oh SB et al, 2001). Szabo et al (2002) reported that chemokine administration into the periaqueductal gray matter inhibits opioid-induced analgesia. Some neurons express CXCR4 and μ-opioid receptors (MORs). Treatment of CXCR4+/MOR+ neurons with the selective MOR agonist DAMGO or peptide endomorphin-1 inhibited intracellular signaling pathways (ERK1/2 and Akt) activated by CXCL12. Furthermore, DAMGO abolished the neuroprotective effect of CXCL12 in N-methyl-d-aspartate (NMDA) neurotoxicity studies. (Patel JP et al, 2006).

6.2. Neurotoxicity/Neuroprotection

Similar experiments to those described in the previous section led to the proposal that neuronal apoptosis induced by HIV-1 gp120 and CXCL12 was mediated by the chemokine receptor CXCR4 (Hesselgesser J et al, 1998). More recent studies showed that gp120 stimulates p53 activity and induces expression of the p53 pro-apoptotic target Apaf-1 in cultured neurons. Gp120 regulates p53 phosphorylation and expression of other p53-responsive genes, such as MDM2 and p21. Meanwhile, CXCL12 promotes neuronal survival, increases p53 acetylation and p21 expression in neurons (Khan MZ et al, 2005). CXCL12 rescues neurons from apoptosis by stimulating the time-dependent increase of total Rb expression while decreasing the nuclear content of phosphorylated (Ser780/Ser795) Rb and the transcriptional activity of E2F-1. Gp120 exerts opposite effects at the nuclear level (Khan MZ et al, 2003). BDNF and FGF reduced the levels of CXCR4, thereby protecting from gp120-mediated neuronal apoptosis (Sanders VJ et al, 2000; Bachis A et al, 2004). However, TNF-α may render neuronal cells vulnerable to the apoptotic effects of HIV by increasing the cell surface expression of CXCR4 (Rostasy K et al, 2005). Gp120 injected into the rat striatum or hippocampus is sequestered by neurons and subsequently retrogradely transported to distal neurons that project to these brain areas. Both retrograde transport of gp120 and apoptosis are dependent on CXCR4 (Bachis A et al, 2006).

Recent studies indicate that gp120 may induce both neuronal apoptosis and axonal degeneration in cultured rat DRG sensory neurons (Melli G et al, 2006). Binding of gp120 to CXCR4 on sensory axons may directly cause the local axonal degeneration. In addition, gp120 triggered the release of chemokine CCL5 from Schwann cells, which caused TNF α-mediated neuronal apoptosis and neuritic degeneration in vitro (Kurry P et al, 2003).

6.3. Intercellular communication

Besides neurons, expression of CXCR4 is detected on the microglia and astrocytes in the mature CNS (Tanabe S et al, 1997; Ohtani Y et al, 1998). CXCL12 induces the migration of mouse microglial cells but not astrocytes (Tanabe S et al, 1997). In vitro, CXCL12 stimulates astrocyte proliferation, associated with sequential activation of a G-protein-PI-3Kinase-ERK1/2 signaling cascade (Bajetto A et al, 2001; Barbero S et al, 2002; Bonavia R et al,

2003). Our lab demonstrated that CXCL12 activates NF-κ B, stimulates production of chemokines and cytokines, and induces cell death in primary astrocytes, effects that depend on ongoing secretion of TNF-α(Han Y et al, 2001a) cAMP and IL-6 have been suggested to induce CXCL12-dependent chemotaxis of astroglia by upregulating the expression of CXCR4 (Odemis V et al, 2002). CXCL12/CXCR4 have been suggested as regulator of complex intercellular neuro-glial or glial-glial interactions. For instance, CXCL12 induces the production of TNF-α in astrocytes. Autocrine/paracrine TNF-α from astrocytes not only results in the glutamate release that directly signals to the astrocytes, but also causes astrocyte derangement when activated microglia cooperate to dramatically enhance release of TNF-α in response to CXCR4 stimulation (Bezzi P et al, 2001).

7. Pathological implications of CXCL12/CXCR4 in human CNS disorders

7.1. HIV-associated encephalopathy

HIV-associated encephalopathy has been one of the most common causes of morbidity associated with infection by HIV-1 (Price RW and Sidtis JJ, 1990) in the absence of particularly effective anti-retroviral treatments. Pathology of HIV-associated encephalopathy is characterized by the loss of subsets of neurons in the cortex, limbic system and basal ganglia (Glass JD et al, 1998). CXCR4 was the first identified coreceptor for T trophic HIV virus that infects CD4+ T-lymphocytes (Feng Y et al, 1996; Lapham CK et al, 1996). CXCR4 is constitutively expressed in the human brain by neurons and microglia. Microglia are the key cell type infected by HIV-1 in the CNS (Gonzalez-Scarano F and Martin-Garcia J, 2005). HIV-1 virus may also enter the CNS via infected monocytes (probably infected by using the CCR5 co-receptor) that traverse the blood brain barrier to replenish perivascular macrophages. Up-regulation of CXCR4 expression has been reported in macrophage/microglia and neurons in AIDS patients (Sanders VJ et al, 1998; Vallat AV et al, 1998; Van der Meer P et al, 2000; Petito CK et al, 2001). HIV-1-infected microglia or macrophages regulate astrocyte CXCL12 production through IL-1β (Peng H et al, 2006), providing ligand for upregulated CXCR4. The abnormal expression of CXCL12 and CXCR4 is consistent with the possibility this complex interactions might contribute to the pathogenesis of HIV-associated encephalopathy.

One line of research suggests that gp120 and CXCL12 could directly induce neuronal degeneration and apoptosis through binding to CXCR4, but that cell death can be reduced through heterologous desensitization of CXCR4 (Hesselgesser J et al, 1998; Meucci O et al, 1998; Corasaniti MT et al, 2001; Bachis A and Mocchetti I, 2003). Another protection mechanism implicates BDNF, which reduced expression of CXCR4, an effect which correlated with the ability of BDNF to reduce gp120 internalization and neuronal apoptosis. Moreover, BDNF directly blocked the neurotoxic effect of CXCL12 (Bachis A et al, 2003; Bachis A and Mocchetti I, 2005). However other studies demonstrated that CXCL12 failed to prevent gp120 neurotoxicity, and in fact induced neuronal apoptosis acting indirectly through glial stimulation (Kaul M and Lipton SA, 1999). Bardi G et al (2006) recently demonstrated as expected that CXCL12 down-regulated CXCR4 as is typical for ligand engagement of GPCRs. Interestingly, gp120 did not change CXCR4 membrane levels. Nevertheless, gp120 was still able to activate intracellular signaling and proapoptotic pathways via CXCR4. High expressing alleles of CXCL12 are associated with protection from HIV-1 pathogenesis (Winkler C et al, 1998). In other studies, HIV-1-infected monocyte-derived macrophage secretions, virus or CXCL12 induced a Gi protein-linked decrease in cAMP and increased IP3 and intracellular calcium. Such effects were partially blocked by antibodies to CXCR4 or removal of virus from MDM fluids. Changes in G-protein-coupled signaling correlated with, but were not directly linked, to increased neuronal synaptic transmission, caspase 3 activation and apoptosis (Zheng J et al, 1999). In anther line of research, Jana A and Pahan K (2004) recently suggested that gp120 may induce neuronal apoptosis through the CXCR4-NADPH oxidase-superoxide-neutral

sphingomyelinase-ceramide pathway. Indirect effects of CXCR4 signaling on neuronal viability have also been explored. In particular, gp120 or CXCL12 can indirectly induce the release of glutamate from activated astrocytes, which can lead to excitotoxic neuronal injury (Bezzi P et al, 2001). They found that binding of gp120 or CXCL12 via CXCR4 in astrocytes activates the intracellular calcium-dependent ERK signaling pathway that leads to the release of TNF-α. Second, in a paracrine/autocrine fashion, TNF alpha binds to TNFR1 on astrocytes, which results in the production of prostaglandin E2 (PgE2) by inducible cyclooxygenase 2 (COX-2). PgE2 leads to increased intracellular calcium, triggering the release of glutamate. At the same time, gp120 or CXCL12 binds microglial CXCR4 to stimulate the production of TNF-α. Interestingly, Taylor DL et al (2005) demonstrated that induction of microglial TNF-α is dependent on the stimulation of mGlu2, which is highly correlated with the microglial neurotoxic phenotype. Further, they found that TNF-α can induce neuronal apoptosis by directly binding to its receptor TNFR1 on the surface of neurons. Bachis A et al (2006) recently reported that cleaved caspase-3 and terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL), hallmarks of apoptosis, were seen in neurons internalizing and transporting gp120. The retrograde transport of gp120 and apoptosis were mediated by the chemokine receptor CXCR4. Besides that, Zhang et al (2003) reported HIV-infected macrophages secrete matrix metalloproteinase-2 (pro-MMP-2), which can be activated by neuronal membrane-type 1 matrix metalloproteinase (MT1-MMP). Activated MMP2 cleaves CXCL12 into a truncated CXCL12 (5–67) by removing its N-terminal tetrapeptide. Truncated CXCL12 (5–67) caused neurodegeneration potentially through binding another chemokine receptor CXCR3 (Zhang et al, 2003; Vergote D et al, 2006).

In summary, signaling to CXCR4 by gp120 is proposed to activate multiple pathways that converge, directly or indirectly on neuronal injury.

7.2. Brain tumors

Brain tumors encompass neoplasms that originate in the brain itself (primary brain tumors) or involve the brain as a metastatic site (secondary brain tumors). The majority of recent research related to CXCR4 focused on primary brain tumors. Up-regulated CXCL12 and CXCR4 were observed in primary brain tumors including glioblastoma; astrocytoma; and medulloblastomas (Sehgal A et al, 1998a; Sehgal A et al, 1998b; Schuller U et al, 2005; Liu G et al, 2006; Woerner BM et al, 2005). While CXCR4 was expressed in tumor cells and some endothelial cells, CXCL12 was present in endothelial cells and infiltrating microglia. By using an antibody that can distinguish activated CXCR4 phosphorylated on serine 339, phospho-CXCR4 was present in tumor cells and vascular endothelial cells in all grades of astrocytoma (Woerner BM et al, 2005). A significant correlation of high CXCR4 mRNA levels and presence of the neurotrophin receptor p75NTR or expression of ATOH1 and GLI1 suggested that CXCR4 is a reliable marker for tumors derived from the cerebellar external granular layer (Schuller U et al, 2005). In astrocytomas, CXCL12 and CXCR4 expression were colocalized when both were expressed, and CXCL12 and CXCR4 expression increased with increasing tumor grade. Two proteins were expressed in regions of angiogenesis and degenerative, necrotic, and microcystic changes (Rempel SA et al, 2000). Expression of CXCL12 was associated with a significantly shorter time to tumor progression (TTP). The data suggest the possible prognostic value for CXCL12 as an angiogenesis- and tumor-growth-related chemokine on TTP in low-grade gliomas (Salmaggi A et al, 2005). CXCL12 induced a significant increase of DNA synthesis in primary human glioblastoma cell cultures and chemotaxis in a glioblastoma cell line (Bajetto A et al, 2006). CXCR4 was increased by VEGF and bFGF, suggesting an angiogenic amplification loop. In tumor microenvironments, CXCL12 is proposed to modulate the proliferation and survival of both endothelial and tumor cells (Salmaggi A et al, 2004). Activation of CXCR4 is critical for the growth of both malignant neuronal and glial tumors. Systemic administration of CXCR4 antagonist AMD 3100 inhibits growth of intracranial

glioblastoma and medulloblastoma xenografts in small-animal models by increasing apoptosis and decreasing the proliferation of tumor cells (Rubin JB et al, 2003).

7.3. Stroke

Stroke is the acute neurologic injury that occurs as a result of brain ischemia due to thrombosis, embolism, or systemic hypoperfusion or due to intracerebral hemorrhage or subarachnoid hemorrhage. In stroke animal models, CXCL12 is increased and released primarily by activated astrocytes and endothelial cells (Ceradini DJ et al, 2004; Hill WD et al, 2004). The elevation of CXCL12 is associated with the infiltration of monocytes to the areas of ischemic injury and potentially mediates neuroinflammatory pathogenesis (Hill WD et al, 2004). Dexamethasone (DEX) down-regulates CXCR4 and exerts neuroprotection in neonatal rats by influencing the inflammatory cascade induced by hypoxia-ischemia in the neonatal brain (Felszeghy K et al, 2004). Previously, Stumm RK (2002) reported that neuronal CXCL12 was transiently downregulated and neuronal CXCR4 was transiently upregulated in the nonlesioned cerebral cortex in response to ischemia. Although the detailed pathological consequences are not clear, the effects would markedly reduce signaling through CXCR4.

Interestingly, CXCL12/CXCR4 has been suggested to regulate the recruitment of hematopoietic NPCs to the injured site, further enhancing the tissue repair during neuronal regeneration. Ceradini DJ et al (2004) demonstrated that up-regulated CXCL12 expression increases the adhesion, migration and homing of circulating CXCR4-positive NPCs to ischemic tissue. Blockade of CXCL12 in ischemic tissue or CXCR4 on circulating NPCs impairs the recruitment of NPCs to sites of injury. Yamaguchi et al (2003) suggested that locally delivered CXCL12 augments vasculogenesis and subsequently contributes to ischemic neovascularization in vivo by augmenting endothelial progenitor cell (EPC) recruitment in ischemic tissues.

7.4. Multiple sclerosis (MS)

MS is an inflammatory demyelinating disorder, which is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring in the CNS (Weiner H, 2004). Experimental allergic encephalomyelitis (EAE) is a murine CD4+ Th1-cell and Th17-cell mediated demyelinating disease of the CNS that serves as a model for inflammatory aspect of human MS (Swanborg RH, 1995; Kleinschek MA et al, 2007). CXCL12 is present in the cerebrospinal fluid (CSF) from patients with MS and other inflammatory neurological disorders (Pashenkov M et al, 2003; Corcione A et al, 2004; Krumbholz M et al, 2006). In active MS lesions, CXCL12 levels were high on astrocytes throughout the lesion areas and on some monocytes/macrophages within vessels and perivascular cuffs, with lesser staining on EC. In silent MS lesions, CXCL12 was detected on EC and astrocytes, particularly hypertrophic astrocytes near the lesion edge (Calderon TM et al, 2006; Krumbholz M et al, 2006). In vitro, IL-1β or myelin basic protein (MBP) induced CXCL12 in astrocytes by signaling pathways involving ERK and PI3-K while human umbilical vein endothelial cell (HUVEC) did not produce CXCL12 after treatment with MBP or IL-1β (Calderon TM et al, 2006). Cultured human astrocytes stimulated with IL-1β and TNF produced CXCL12 and other chemokines (Ambrosini E et al, 2005). In EAE animals, increased level of CXCR4 was reported in CNS parenchymal cells (Jiang Y et al, 1998; Glabinski AR et al, 2000). These descriptive observations were extended by McCandless et al (2006) who demonstrated that inhibition of CXCR4 activation during the induction of EAE led to loss of the typical intense perivascular cuffs, which were replaced with widespread white matter infiltrationof mononuclear cells, worsening the clinical severity of the disease. However, the detailed roles of CXCL12 in CNS autoimmunity remain to be comprehensively determined.

8. Summary

Chemokine CXCL12 critically regulates an enormous diversity of processes in both CNS and peripheral immune system, including migration; survival; proliferation; and intercellular communication. Although many functional features appear to be shared in common between the CNS and the immune system, the detailed roles of CXCL12 in the CNS are not simply duplicated from the peripheral immune system. To the contrary, the involvement of CXCL12 and CXCR4 suggests that this ligand-receptor pair is required for CNS homeostasis. Additionally, CXCL12 and CXCR4 have been implicated in the pathogenesis of various neurodegenerative and neuroinflammatory diseases, making them valuable targets for drug development.

Acknowledgements

Abrreviations

ADC
AIDS dementia complex

AIDS
acquired immunodeficiency syndrome

AKT
v-akt murine thymoma viral oncogene homolog

AVP
arginine vasopressin

BDNF
brain-derived neurotrophic factor

bFGF
basic fibroblast growth factor

CDK-5
cyclin-dependent kinase 5

CNS
central nervous system

COX-2
cyclooxygenase 2

CR cell
Cajal-Retzius cell

DG
dentate gyrus

EAE
experimental allergic encephalomyelitis

EC

endothelial cell

EGL

external granular layer

EPC

endothelial progenitor cell

EPSC

excitatory postsynaptic currents

ERK

extracellular signal-regulated kinase

Gαi

inhibitory Gα protein isotypes

GCL

granule cell layer

GnRH

gonadotropin-releasing hormone

GPC

cerebellar granule precursor cells

GPCR

G protein-coupled receptor

GTP

guanosine triphosphate

GRK

G protein-coupled receptor kinase

HIF-1

hypoxia-inducible factor-1

HIV-1

human Immunodeficiency virus

HPC

hematopoietic progenitor cell

HSPG

heparan sulfate proteoglycans

HUVEC

human umbilical vein endothelial cell

IGL

internal granule layer

IL-1β interleukin 1

beta

IL-6

interleukin 6

IP3

inositol 1, 4, 5 trisphosphate

IZ

intermediate zone

JAK/STAT

janus kinase-signal transducer and activator of transcription

JNK

Jun N-terminal kinase

LTP

long-term potentiation

MAM

methylazoxymethanol

MAPK

mitogen-activated protein kinase

MBP

myelin basic protein

MMP-2

metalloproteinase-2

MOR

μ-opioid receptor

MS

multiple sclerosis

MT1-MMP

membrane-type 1 matrix metalloproteinase

MZ

marginal zone

NKκB

nuclear factor kappa-B

NMDA

N-methyl-d-aspartate

NPC

neural progenitor cell

PGC

primordial germ cell

PgE2

prostaglandin E2

PI3K

phosphoinositide-3 kinase

PLC

phospholipase C

PLL

> posterior lateral line

PNS

> peripheral nervous systems

PTX

> bordetella pertussis toxin

PyK2

> protein tyrosine kinase 2 beta

QUIN

> quinolinic acid

SGZ

> subgranular zone

SHH

> sonic hedgehog

SVZ

> subventricular zone

TgSG

> trigeminal sensory ganglia

TNF-α

> tumor necrosis factor alpha

VEGF

> vascular endothelial growth factor

VEGF

> vascular endothelial growth factor

VNO

> vomeronasal organ

VZ

> ventricular zone

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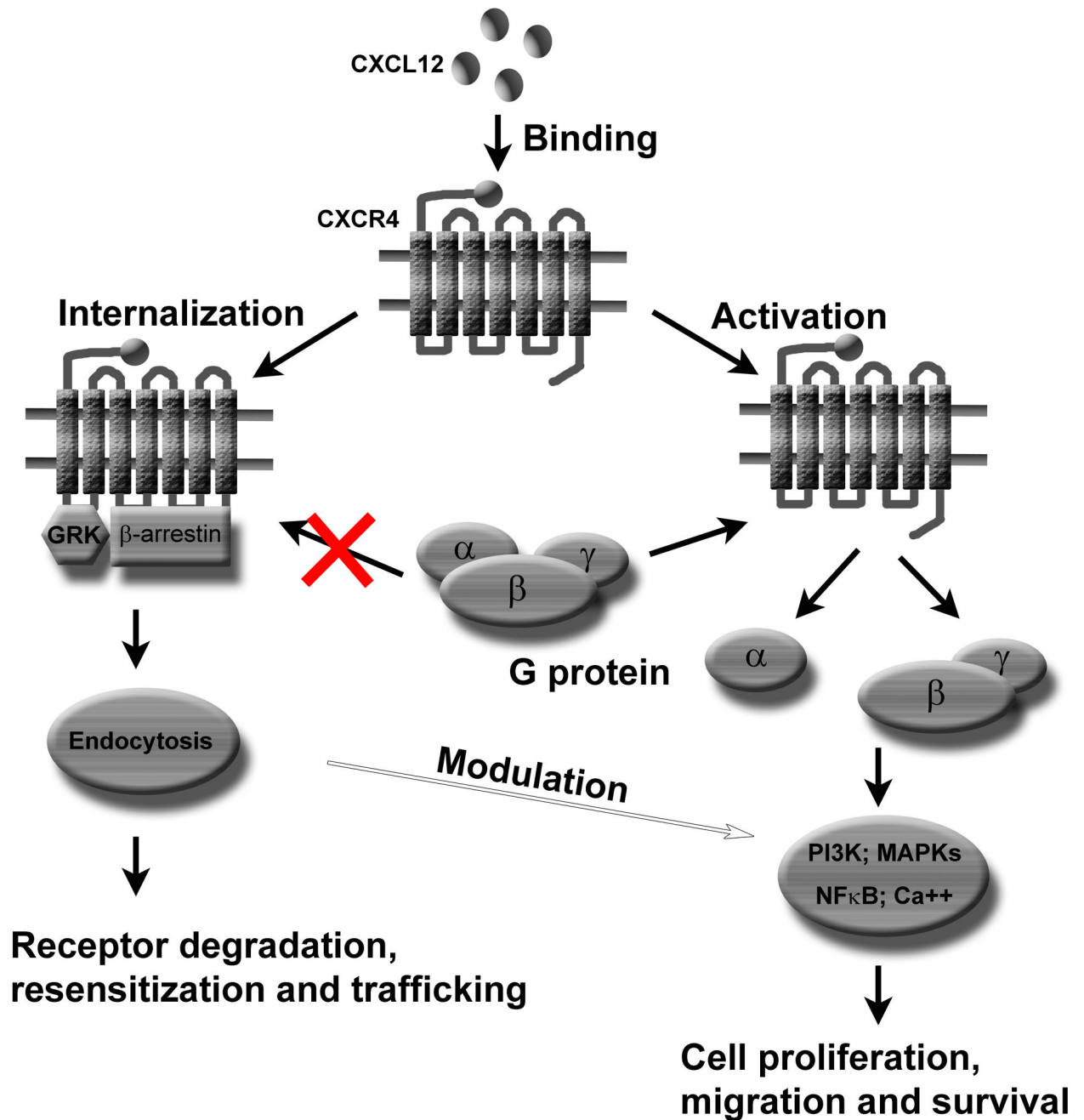
Fig. 1. CXCL12/CXCR4 signaling pathways and their regulation
Binding of CXCL12 to CXCR4 activates multiple G-protein-mediated signaling pathways
(such as PI3K, MAPKs and NFκB) and induces the release of intracellular Ca^{2+}. These
signaling pathways are involved in cell proliferation, migration and survival or apoptosis.
Activation of CXCR4 leads to GRK/β-arrestin-mediated receptor desensitization and prevents
CXCR4 from further interacting with G proteins. GRK/β-arrestin promotes clathin-dependent
endocytosis that is coupled to receptor trafficking, degradation and resensitization. β-arrestin2
may modulate CXCR4-mediated activation of p38 MAPK signaling pathway.
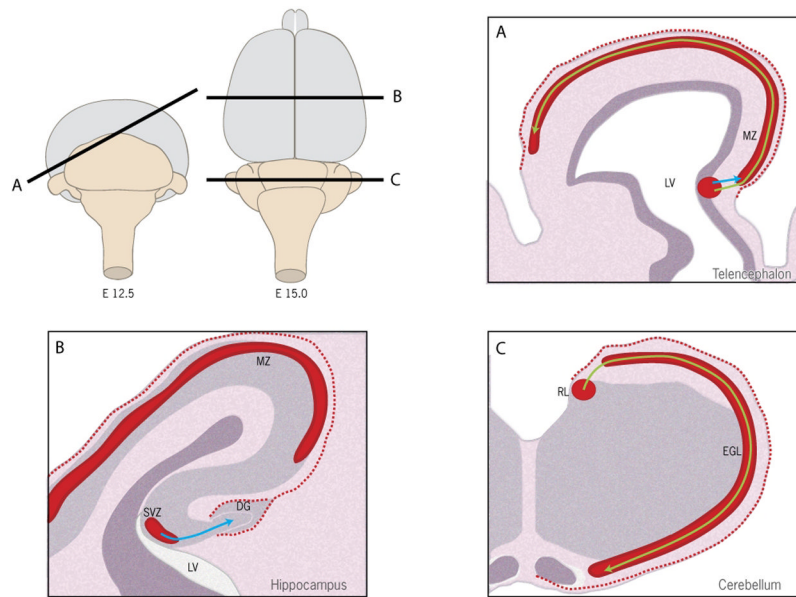
Fig. 2.
Roles of CXCL12/CXCR4 in brain development. The cartoon shows a schematic view of developing mouse brain (E12.5 and E15). CXCL12/CXCR4 regulates the migration of neuronal precursors during early brain development. (A) At embryonic day 12.5 (E12.5), CXCR4+ Cajal-Retzius (CR) cells are generated from the ventricular zone (VZ) near the lateral ventricle (LV) of the telencephalon and migrate to the marginal zone (MZ) through short range radial migration (blue arrow). CXCR4+ CR cells further spread to the whole telencephalon through long range tangential migration (yellow arrow). CXCL12 secreted from the meninges (dashed red line) is required for the migration of CR cells; (B) In E15 hippocampus, CXCR4 + dentate precursors are generated from subventricular zone (SVZ) near the lateral ventricle (LV). CXCL12 secreted from the meninges (dashed red line) guides the migration (blue line) of dentate precursors to the dentate gyrus (DG); (C) In E15 cerebellum, CXCR4+ granule cell precursors that are generated from the subventricular zone (SVZ) of rhombic lip (RL) migrate tangentially (yellow arrow) to cover most of the cerebellar surface forming the external granule cell layer (EGL). CXCL12 (dashed red line) secreted from meninges maintains cell proliferation and prevents premature exit of granular cell precursors from the EGL.