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CXCR4/CXCR7 Molecular Involvement in Neuronal and Neural Progenitor Migration: Focus in CNS Repair

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In the adult brain, neural progenitor cells (NPCs) reside in the subventricular zone (SVZ) of the lateral ventricles, the dentate gyrus and the olfactory bulb. Following CNS insult, NPCs from the SVZ can migrate along the rostral migratory stream (RMS), a migration of NPCs that is directed by proinflammatory cytokines. Cells expressing CXCR4 follow a homing signal that ultimately leads to neuronal integration and CNS repair, although such molecules can also promote NPC quiescence. The ligand, SDF1 alpha (or CXCL12) is one of the chemokines secreted at sites of injury that it is known to attract NSC-derived neuroblasts, cells that express CXCR4. In function of its concentration, CXCL12 can induce different responses, promoting NPC migration at low concentrations while favoring cell adhesion via EGF and the alpha 6 integrin at high CXCL12 concentrations. However, the preclinical effectiveness of chemokines and their relationship with NPC mobilization requires further study, particularly with respect to CNS repair. NPC migration may also be affected by the release of cytokines or chemokines induced by local inflammation, through autocrine or paracrine mechanisms, as well as through erythropoietin (EPO) or nitric oxide (NO) release. CXCL12 activity requires G-coupled proteins and the availability of its ligand may be modulated by its binding to CXCR7, for which it shows a stronger affinity than for CXCR4.

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Neuronal progenitor cells (NPCs) can differentiate into neurons, astrocytes or oligodendrocytes, and they can promote the survival/integration of cells into new neuronal circuits after CNS insult (Fallon et al., 2000). Neurogenesis occurs in specific areas of the brain (Altman and Das, 1965), including the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the granular cell layer (Gould et al., 1999; Bernier et al., 2002; Gould, 2007 Coremans et al., 2010; Pignatelli and Belluzzi, 2010; Walton et al., 2013). Functional recovery from insult requires the integration of new

Abbreviations: AMD3100, plerixafor; AMPc, cyclic AMP; Ang-1, angiopoietin; BBB, blood-brain barrier; BRAK/CXCL14, breast- and kidney-expressed chemokine/CXC chemokine ligand 14; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CCL2/MCP-1, monocyte chemotactic protein-1; $CD34^+$, hematopoietic progenitor cell antigen; CXCR4, (C-C motif) receptor 4; CCR5, (C-C motif) receptor 5; CNTF, ciliary neurotrophic factor; CREB, (cAMP response element-binding protein); Cux1/2, cut-like homeodomain transcription factor family 1/2; CXCR6, Chemokine (C-X-C motif) receptor 6; CXCL12 CXCL12 (SDF1 alpha), stromal cell derived factor 1 alpha; EGF, epidermal growth factor; EFGR, Epidermal growth factor receptor; EPO, erythropoietin; FGF-2, basic fibroblast growth factor-2; GCL, granular cell layer; GABA, gamma-aminobutyric acid; GFAP, glial fibrillary acidic protein (GFAP); ICAM, intercellular adhesion molecule-1; LIF, leukemia inhibitory factor; Il-8, interleukin 8; IL-1Beta, interleukin-1 beta (IL-1β); I-TAC, interferon–inducible T cell alpha chemoattractant; IFN gamma, Interferon gamma; G-CSF, granulocyte colony-stimulating factor; HSC, hepatic stellate cells; LFA-1, lymphocyte function-associated antigen 1; MBEC, mouse brain endothelial cells; MAPK/CREB, mitogen-activated protein kinase/cAMP response element-binding protein; MMP2/9, metalloproteinase 2/9; PDGF, platelet-derived growth factor; NGF, nerve growth factor; NO, nitric oxide; NPC, neural progenitor cells; PC, preconditioning; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; OB, olfactory bulb; PCNA, proliferating cell nuclear antigen; PSA-NCAM, polysialylated neuronal cell adhesion molecule; RMS, rostral migratory stream; si-RNA (CXCR4), RNA interference (CXCR4); SGZ, subgranular zone; SVZ, subventricular zone; rhEPO, human recombinant erythropoietin; VEGF, vascular endothelial growth factor.

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neurons into the existing and/or damaged circuits, which depends on their correct migration (Decimo et al., 2012). Under non-pathological conditions, most NPCs can produce interneurons in the olfactory bulb (OB): (Christie and Turnley, 2013; Walton et al., 2013), and new neurons are derived from less-differentiated neural stem/progenitor cells (NSCs) and neuroepithelial cells (NEPs) that differentiate into neuronal-restricted or glial-restricted precursor cells (Bonaguidi et al., 2005, 2008; Stephens et al., 2012). NPCs express nestin (a neuroepithelial cell marker) and musashi-1, a neural RNA binding protein, while undifferentiated NEPs express specific transcription factors, such as Sox1, Sox2, and Sox3 (Foshay and Gallicano, 2008; Sundberg et al., 2011).

Which Signals Induce NPC Migration toward Damaged Areas of the CNS?

Several extrinsic and intrinsic factors that emanate from the SVZ can regulate neurogenesis when inflammation arises as a result of CNS damage (Whitney et al., 2009; Gonzalez-Perez et al., 2010; Boneva and Yamashima, 2012; Gensel et al., 2012). Many such factors regulate the fate and proliferation of NSCs in the neurogenic niches, including nerve growth factor (NGF), bFGF (basic fibroblast growth factor) or FGF-2 (basic fibroblast growth factor) (Schwindt et al., 2009; Bohrer and Schwertfeger, 2012), BDNF (brain-derived neurotrophic factor) (Zhang et al., 2011), Neurotrophin-4/5 (NT3 and NT4/5), ciliary neutrophic factor (CNTF), vascular endothelial growth factor (VEGF), erythropoietin (EPO), leukemia inhibitory factor (LIF) (Oshima et al., 2007), BMI-1 and platelet-derived growth factor (PDGF-α) (Lowenstein and Arsenault, 1996; Jo et al., 2000; Kijowski et al., 2001; Coskun and Luskin, 2002; Aguirre et al., 2005; Bonaguidi et al., 2005; Bauer and Patterson, 2006; Liu et al., 2006; Dempsey and Kalluri, 2007; Covey and Levison, 2007; Liu et al., 2007; Krüger et at., 2007; Bonaguidi et al., 2008; Choi et al., 2008; Lum et al., 2009; Leong and Turnley, 2011; Reed et al., 2012; Koivuniemi et al., 2013; Talaverón et al., 2013; Sánchez-Mendoza et al., 2013). In this review, we shall examine how chemokines influence NPC migration within the SVZ following injury and CNS damage (Wang et al., 2002; Imitola et al., 2004; Merino et al., 2011a). Chemotactic factors promote neurogenesis and gliogenesis in the normal developing brain (Réaux-Le Goazigo et al., 2013), and the CXCR4/CXCL12 (SDF1) axis induces NPC differentiation and migration in the periinfarct area (Imitola et al., 2004; Dziembowska et al., 2005; Tran et al., 2007; Turbic et al., 2011). The response of SVZ-derived NPC, and of the new cells they produce, is quite variable, depending on the type of injury, the brain area damaged and the trophic factor/s released following damage, such as cytokines (Hagberg and Mallard, 2005), chemokines (Bonecchi et al., 2009) or vascular factors (Schanzer et al., 2004; Bauer, 2009). Thus, cell therapy could possibly promote the migration of SVZ neuroblasts that express the CCR1-8, 10 and/or CXCR1-6 chemokine receptors and their ligands (Tran et al., 2007). Most of the research into chemokines has been carried out in rodent models, studying the ectopic migration and neural differentiation of SVZ-derived NPCs following the neural damage produced by cerebral ischemia (Li et al., 2012; Lindvall et al., 2004; Lichtenwalner and Parent, 2006). In these models, the enhanced NPC motility induced by chemokines and growth factors guides neuroblasts from the SVZ/RMS toward the damaged areas in the CNS (Merino et al., 2008, 2011b; Turbic et al., 2011), with CXCR4 co-localizing with PSA-NCAM in the migrating cortical neurons (Merino et al., 2008). Some chemokines have anti-apoptotic effects and they promote neurogenesis in rodent models of cerebral ischemia (Imitola et al., 2004; Liu et al., 2007, 2008a,b; Merino et al., 2011a). Consequently, both endogenous and grafted NPCs can migrate and differentiate into new neurons according to different chemotactic gradients (Li et al., 2013; Liu et al., 2008). The signaling mechanisms by which chemokines regulate differentiation, cell remodeling and self-repair in pathological circumstances in the CNS may potentially promote recovery to some extent (Bye et al., 2012; Gensel et al., 2012; Hassani et al., 2012). Indeed, proliferation is a feature associated with stem cell transplantation during the first week post-lesion in rodent models of global ischemia (Levison et al., 2001; Chen et al., 2001, 2004; Bonecchi et al., 2009). However, the poor survival of new neurons in the lesioned area (Arvidsson et al., 2002), together with the limited integration of newly-formed cells into existing neural circuits more than four weeks after their implantation, are issues that limit the efficacy of cell therapy in neurodegenerative diseases (Aboody et al., 2000; Stroemer et al., 2009; Perederiy et al., 2013). In fact, several weeks after transplantation proliferation rates return to normal (Thored et al., 2006; Kokaia and Lindvall, 2003). Thus, it is crucial to elucidate how chemokines direct neuroblast migration and the interaction of these cells with their environment (Robin et al., 2006; Tiveron et al., 2006; Barkho and Zhao, 2010), particularly in a neuropathological context (Fiala et al., 2012).

In the present review, we will concentrate on how molecular regulators of the CXCR4/CXCR7/CXCL12 regulate NPC migration and CNS repair, and the extent to which crosstalk between the nervous and immune systems might regulate these processes (Klein and Rubin, 2004). Several chemokines are expressed in the vascular niche (CCR1–3, 5, 7–10 and CXCR1–4), as well as in neurospheres (CCR1–8, 10 and CXCR1–6: (Tran et al., 2007; Bonecchi et al., 2009). Chemotactic factors direct NPC migration after striatal damage, these include monocyte chemoattractant protein-1 (MCP-1, CCL-2), and growth regulated oncogene-alpha (GRO alpha) (Gordon et al., 2009). Interestingly, CXCR4 signaling induces survival and migration of neural and oligodendrocyte precursors (OP) during embryonic and postnatal CNS development. In fact, in CXCR4-defective mice, the number of neural precursors in the neurosphere outgrowth was twofold less than in wild-type mice; Neural precursor radial cell migration was also decreased in these mices (Lu et al., 2002; Dziembowska et al., 2005). However, the addition of recombinant CXCL12 protein to neurospheres derived from wild type mice increases the radial migration of cells from the sphere in a dose-dependent manner (Dziembowska et al., 2005). In these studies, fewer differentiated oligodendrial cells expressing platelet-derived growth factor receptor (PDGFR) were found in the CXCR4-deficient mice (Dziembowska et al., 2005). These observations support a role for chemokines in NPC migration and repair. Indeed, the release of CXCL12 and its interaction with CXCR4 promotes migration from neurospheres derived from E17 embryonic or adult mouse NPCs (Robin et al., 2006) Figure 1A shows neurosphere cultures at 5 days in vitro and Figure 1b and c indicates neuroblast and immature neurons derived from them.

Chemokines are small chemotactic cytokines that interact with specific G-protein coupled receptors (CCR., CXCR, CX3CR, CR) and regulate leukocyte or immune cell trafficking to damaged areas of the CNS (Asensio and Campbell, 1999). Proinflammatory cytokines act as neuromodulators/neurohormones, and they can regulate processes such as synaptic transmission (Banisadr et al., 2011), migration, and NPC proliferation by providing autocrine/paracrine survival signals (Rostene et al., 2007); Figure 2 shows all regulators of CXCR4. For instance, other BRAK/CXCL14 chemokines also regulate synaptic transmission in the adult dentate gyrus (Banisadr et al., 2011). The chemokine BRAK (CXCL14) is an ancient member of the chemokine family whose functions in the brain are completely unknown. CXCL14 is a small cytokine

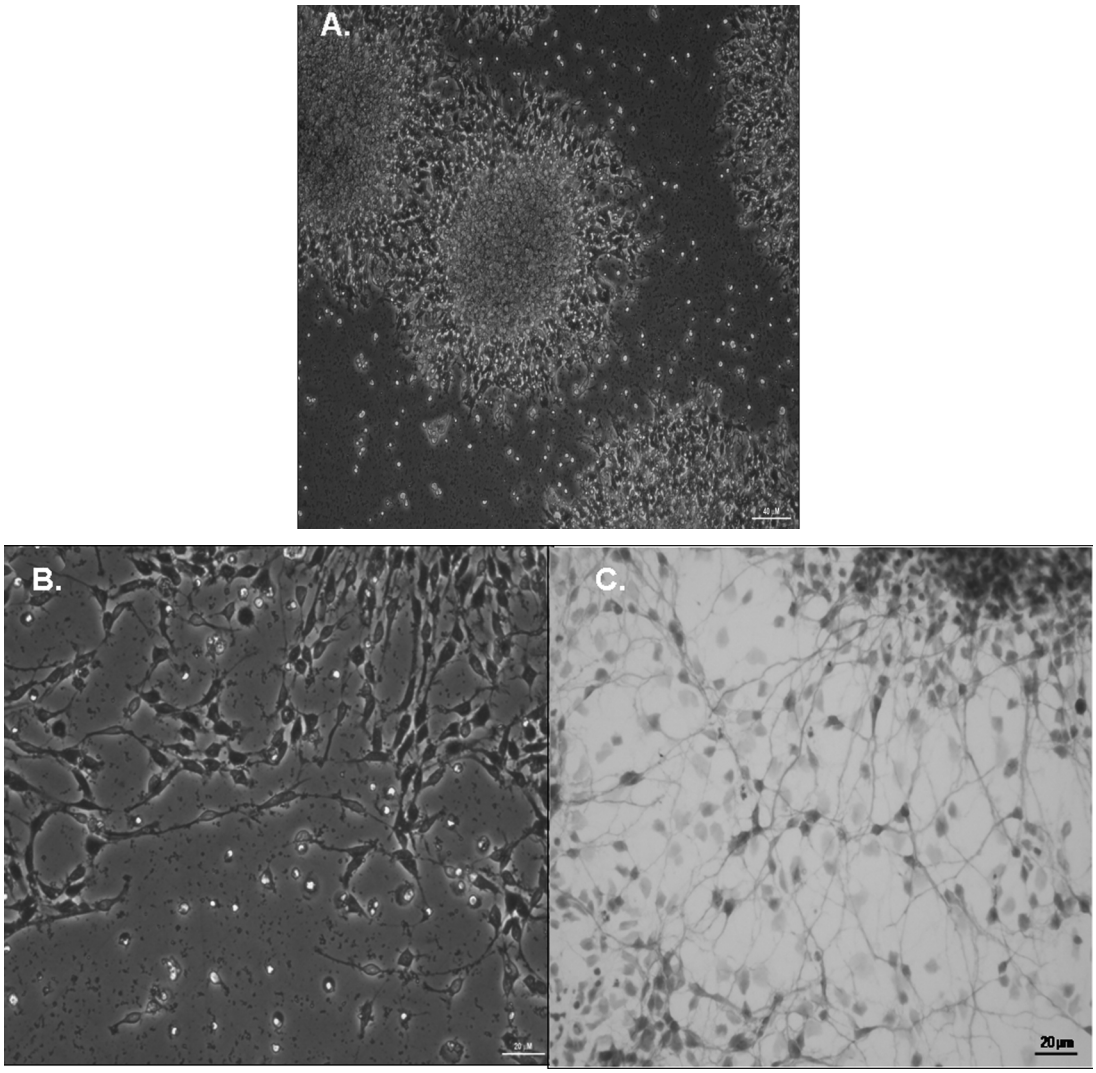

Fig. 1. (A) SVZ Neurospheres after 5 days of differentiation in primary culture. Phase-contrast image of neurosphere with cells invading the space between them. (B,C) Neuroblasts and immature neurons in vitro at 5 days of culture.

belonging to the CXC chemokine family that is also known as BRAK (for breast and kidney expressed chemokine). Chemokines can also regulate the capacity to adapt migratory patterns in response to changes in the surrounding environment (Otto et al., 2002; Hallbergson et al., 2003; Ji et al., 2004b; Bye et al., 2012). Neurogenesis via the CXCR4/CXCL12 interaction, and that provoked by other chemokines (e.g., monocyte chemotactic protein 1 [CCL2] [Li et al., 2008]), induces the migration and differentiation of NPCs within the SVZ in periinfarct areas following cerebral ischemia (Arvidsson et al., 2002; Zhang et al., 2002; Ni et al., 2004; Robin et al., 2006; Ohab et al., 2006; Liu et al., 2008). However, chemokines such as CXCL12 or CX3CL1/fractalkine can promote NPC quiescence (qNPC) (Krathwohl and Kaiser, 2004a,b), as well in hematopoietic stem cells (HSCs; Broxmeyer et al., 2003).

Do NPCs Promote Functional Recovery in Neurogenic Areas Following CNS Insult?

The transition from quiescence to self-renewal or differentiation is a response to specific cues or factors (Kiel and Morrison, 2008; Christie and Turnley, 2013). For example, two weeks after injury, newly-generated neuroblasts re-route from the SVZ and RMS to the lesion, where they can differentiate to form mature neurons in rodents (Lindvall et al., 2004; Kokaia et al., 2012; Kokaia and Lindvall, 2013). These SVZ-derived neuroblasts can replace damaged neurons in the hippocampus, striatum, and neocortex (Takasawa et al., 2002; Jin et al., 2005; Tonchev et al., 2005; Kuge et al., 2009), and they can differentiate into neurons, oligodendrocytes, or astrocytes. The NPCs that originate in the SGZ can be identified by a combination of brain lipid binding protein (BLBP), nestin and glial fibrillary acidic protein (GFAP), and most NPCs express the markers Nestin and Sox2 (Ilieva and Dufva, 2013). Subsequently, the majority of these NPCs differentiate into immature doublecortin positive (DCX+) neurons (or neuroblasts) and mature NeuN+ neurons, which can integrate into hippocampal networks as fully functional neurons (Bye et al., 2012; Lacar et al., 2012).

The SVZ is a three-dimensional interconnected niche that is made up of three major cell types (Lacar et al., 2012). The formation and proliferation of NPCs is dependent on the Sox

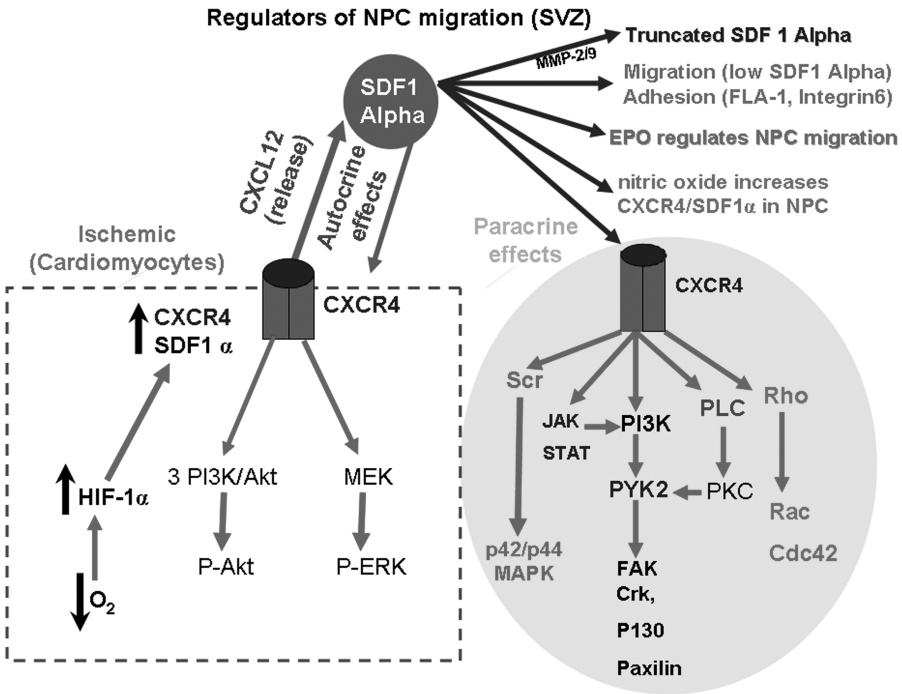

Fig. 2. Molecular modulators of CXCR4/CXCR7 chemokines in neuronal repair and neuroblast recuruitment. SDF1 Alpha (CXCL12) can induce NPC migration at low concentrations while favoring cell adhesion via EGF and the alpha 6 integrin (at high CXCL12 levels). Cytokines/chemokines regulate NPC migration through autocrine/paracrine mechanisms. In addition, erythropoietin (EPO) or nitric oxide release (NO) release also regulate CXCR4/CXCL12 axis. Finally, CXCL12 activity requires G-coupled proteins and its availability may be modulated by its binding to CXCR7. For instance, hypoxia increases CXCR4/CXCL12 levels (left part) while CXCL12 can induce p-akt or p-ERK cascades (CXCR4 +) (left part) or activate other signaling pathways in cardiomyocytes (Jak/Rho/PKC, right part). CXCL12/CXCR4 signal axis plays pleiotrophic effects (right part). Molecular CXCR4/CXCR7 regulators (upper part).

gene family, in particular Sox2 (Andreu-Agullo et al., 2011). Neuroblasts (DCX+ type A cells) are organized into a network that is ensheathed by the processes of qNSCs (nestin+ and GFAP+ type B cells) and that arises from rapidly amplifying NPCs (Nestin+ and GFAP+ type C cells (Kim et al., 2007; Leong and Turnley, 2011; Saaltink et al., 2012).

In the adult SVZ, NPCs are associated with ependymal and vascular niches that regulate stem cell self-renewal and differentiation. Activated type B stem cells and their progeny (Lacar et al., 2012), the transitory amplifying type C cells, express epidermal growth factor receptor (EGFR) (Abhold et al., 2012), and are most strongly associated with vascular cells (Miller and Gauthier-Fisher, 2009). Adult qNSCs (type B cells) in the SVZ and subgranular zone (SGZ) share basic properties with embryonic radial glia (RG: Miller and Gauthier-Fisher, 2009), and upon transplantation into neurogenic areas of the adult brain (the hippocampus and (OB), these NPCs can differentiate into new neurons in response to local signals released by neurons following CNS insult (Carbajal et al., 2010; Bye et al., 2012).

The development of the CNS requires the formation of numerous, precise connections between neurons and their targets. Newly born neurons from the neocortex can undertake radial migration through the embryonic cortex, whereas tangential migration is a glial-guided process of neuronal translocation that occurs throughout the developing brain but that only persists in the RMS of adult brains (Boldajipour et al., 2008; Christie and Turnley, 2013). These neuroblasts migrate long distances from the SVZ to the olfactory bulb through a glial tunnel formed by astrocytes (Snapyan et al., 2009; Fig. 3). Both actively dividing type B and type C cells are closely associated with the vascular niche in the SVZ (Shen et al., 2008; Tavazoie et al., 2008). Rapidly dividing type C cells give rise to type A neuroblasts, progenitors that divide as they migrate, usually in cell chains. In the dorsal SVZ, neuroblast chains often run parallel to blood vessels in the direction of the RMS (see Fig. 3: Shen et al., 2008; Tavazoie et al., 2008) and the OB (Snapyan et al., 2009). Upon arrival at the OB, neuroblasts switch to radial migration in order to reach their final destination. However, a cortical injury may

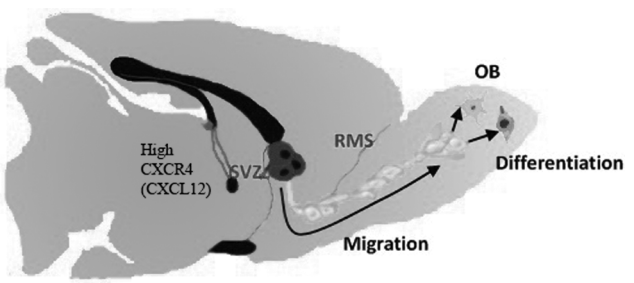

Fig. 3. Scheme of the neural cell migration process from the Subventricular zone (SVZ) toward the olfactory bulb (OB).

change the migration patern switching it from tangencial to radial migration (Goings et al., 2004).

In the CNS, CXCL12 chemokine directs migration to the cerebellum (Ma et al., 1998) or granular cell layer (Lu et al., 2000; Bagri et al., 2002; Tran et al., 2007). In addition, CXCL12 signaling is required for the maintenance of Cajal-Retzius cell position in the marginal zone during normal cortical development (Paredes et al., 2006; Berger et al., 2007). The CXCR4/CXCR7/CXCL12 axis also directs cortical neuronal migration (Tham et al., 2001; Stumm et al., 2003; Li et al., 2008; López-Bendito et al., 2008; Tiveron and Cremer, 2008); CXCL12 is overexpressed by GABAergic neurons from the SVZ GABAergic neurons from the SVZ (Bhattacharyya et al., 2008; Casoni et al., 2012). Indeed, ectopic migration in the granular cell layer occurs in transgenic mice lacking CXCR4 (Lu et al., 2002). CXCR4 is expressed by dividing NPCs from the SGZ, as well as by their derivatives, including doublecortin-expressing neuroblasts and immature granule cells (Bhattacharyya et al., 2008). CXCL12 induces post-synaptic transmission in parvalbumin-containing GABAergic interneurons (basket cells from the dentate gyrus). CXCL12 was located in the synaptic vesicles of basket cells and in GABA-containing vesicles, which suggests that CXCL12 regulates the strength of the GABAergic inputs to the pool of dividing neural progenitors from the dentate gyrus (Bhattacharyya et al., 2008), and that CXCL12 signaling directly regulates the migration of neuroblasts within the RMS (Kokovay et al., 2011). Axonal processes from differentiated neurons are guided to their targets by families of repellent and attractant signaling molecules (Tessier-Lavigne and Goodman, 1996; Yu and Bargmann, 2001). Interestingly, CXCL12 plays an important role in modulating axonal responsiveness to several guidance cues through CXCR4 and a cyclic nucleotide-dependent (AMPc) signaling pathway (Chalasani et al., 2003a,b).

Chemokines like CCL2 direct the migration of NPCs in neuroinflammatory conditions (Belmadani et al., 2006). The CXCR4/CXCL12 chemokine attracts HSCs (hematopoietic stem cells) to pass from the blood to the bone marrow, and it retains stromal cells within the bone marrow niche (Voermans et al., 2001a,b; Chute, 2006; Chu et al., 2007; Rose et al., 2008). CXCL12-induced progenitor migration in hematopoietic progenitor cells bearing CXCR4 chemokine receptor (Voermens et al., 2001a). Stromal cell secretion of CXCL12 creates a gradient that leads to actin polymerization and integrin overexpression, resulting in chemotaxis toward the source of the CXCL12 (Voermans et al., 2001a,b).

Protective actions mediated by immune cells though chemokine release could regulate responses in the neural microenvironment that promote tissue repair in damaged areas of the CNS (Klein and Rubin, 2004; Giusto et al., 2013). On the other hand, through CXCL12 release, the CXCL12–CXCR4 axis regulates the recruitment of endothelial progenitors (CD34+) during inflammation (Modle et al., 1998; Jo et al., 2000). In this context, CXCL12 might enhance the immune and CNS systems during immune and CNS development, favoring their co-ordinated activity (Klein and Rubin, 2004).

Does CXCL12 Regulate the Adherence of NPCs to Blood Vessels and/or Their Migration Along Chemotactic Gradients?

Through different signaling pathways, CXCL12 is involved in regulating quiescence, activation, migration, and homing (Krathwohl and Kaiser, 2004a,b; Wong and Korz, 2008). CXCL12 regulates stem cell migrations that occupy and leave niches in different vascularized parenchymal regions of the CNS. In normal conditions, the cells in these niches can be co-opted to enhance repair when NSCs home to the vasculature through an CXCL12/CXCR4 dependent mechanism. NPCs can become integrated when transplanted into the adult SVZ or hippocampus, and they generate neurons via CXCL12 (Gage et al., 1995; Belmadani et al., 2005), as well as binding preferentially to endothelial cells in function of a chemotactic gradient (Warner et al., 2008).

CXCL12 is a chemoattractant for cortical neurons and meningeal cells (Borrell and Marín, 2006), although it also induces cortical migration (Tham et al., 2001; Lazarini et al., 2003; Stumm et al., 2004; Tissir et al., 2004; Daniel et al., 2005). Indeed, CXCL12 promotes NPC migration within the SVZ along endothelial cells depending on the available CXCL12 and CXCR4 (Zhu et al., 2002). CXCL12 is secreted by meningeal cells and acts as a chemotactic factor for NSCs in the external cerebellar granular layer, as well as for NPCs (Reiss et al., 2002) and hematopoietic precursors (Aiuti et al., 1997). Interestingly, CXCL12 deficiency induces ectopias in the cerebellum, suggesting that perhaps CXCL12 chemotactically attracts neuronal cells isolated from the cerebellar external granular layer (EGL), but not from the internal granular cell layer (IGL) (Reiss et al., 2002). These CXCL12 mediated chemoattractant effects were abolished by removal of CXCL12 from conditioned media by immunoprecipitation, and they could be restored by the addition of recombinant CXCL12 (Reiss et al., 2004). These findings indicate the relevance of the chemoattractant capacity of CXCL12 for neurons (Reiss et al., 2004).

CXCL12 and CXCR4 are involved in actin reorganization and the cell migration mediated by endothelial progenitor cells after PAR-1 activation (Smadja et al., 2005). CXCL12 is the most important chemoattractant for hematopoietic stem/progenitor cells (Aiuti et al., 1997; Kucia et al., 2005) since CXCR4 blockade by AMD3100 (a chemokine blocker), or CXCR4 knockdown by siRNA CXCR4, effectively blocks homing of activated type B and type C cells to blood vessels (Aiuti et al., 1997; Kucia et al., 2005). Cells expressing CXCL12 are found in the SVZ and they express the PCNA cell-cycle marker. Indeed, proliferating CXCL12 cells co-localize with the nuclear Cux1/2 marker exclusively in the SVZ/IZ and cortex (Tiveron et al., 2006; Cubelos et al., 2008), and they play a role in cortical migration and dendritogenesis (Nieto et al., 2004 Cubelos et al., 2010). Collectively, these findings demonstrated the relevance of CXCR4/CXCR7 (SDF1) alpha chemokines in neuronal migration (Wang et al., 2011).

How do Niche-dependent CXCL12 Levels Induce Stem-cell Differentiation and Adhesion, and Promote Cell Migration after CNS Damage?

Curiously, high CXCL12 levels in the ependymal layer could help induce quiescence, as occurs in vascular cells (Siegenthaler and Pleasure, 2010). The differential CXCL12 gradient could regulate NPC quiescence when CXCL12 is abundant, especially since CXCR4 can induce fast desensitization and internalization of this alpha chemokine receptor (Sánchez-Martín et al., 2013). Conversely, low CXCL12 levels induce differentiation and proliferation in the SVZ (Dar et al., 2005; Lapidot et al., 2005). In fact, CXCL12 strongly upregulates EGFR (epidermal growth factor receptor) and alpha6 integrin in activated type B and type C cells, enhancing their activated state and their ability to bind laminin in the vascular niche (Siegenthaler and Pleasure, 2010: Fig. 4). Once SVZ type B stem cells become activated and express EGFR, they are chemically attracted to the surface of blood vessels. It is seems that the upregulation of EGFR in activated type B cells by CXCL12 favors chemotaxis (Porcile et al., 2005; Abhold et al., 2012). CXCL12 can induce SVZ migration via EGFR since crosstalk between EGFR and CXCR4 signaling promotes proliferation (Porcile et al., 2005; Guo et al., 2007). Thus, CXCL12 increases

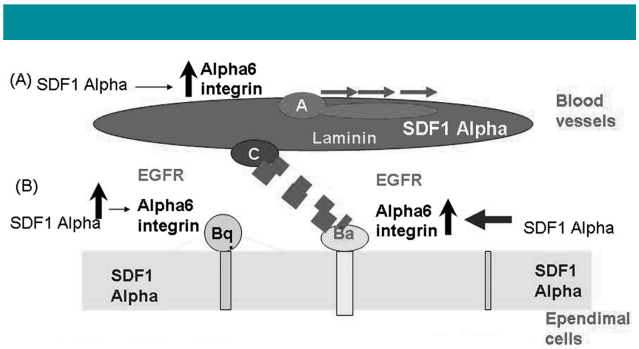

Fig. 4. (A) Stem cell niche quiescent B cells (Bq) are in a subependymal position with their apical process contacting the ventricular space. (B) Once activated (Ba), these cells generate transiently amplifying C cells positioned in close proximity to blood vessels. Both the ependyma and vessels express SDF1 alpha (CXCL12), which regulates proliferation through EGFR and cell ahdhesion (α6β1, integrin). C cells generate A cells, which them migrate toward the olfactory bulb (OB) through the rostral migratory stream (RMS).

the motility of type A neuroblasts and induces NPC migration from the SVZ toward the OB (Kokovay et al., 2010; Siegenthaler and Pleasure, 2010). Consequently, CXCL12 regulates progenitor cell occupancy and exit from the adult SVZ through its activity within vascular niches (Siegenthaler and Pleasure, 2010; Fig. 4).

Alternatively, CXCL12 is concentrated by heparan sulfate proteoglycans (Amara et al., 1999; Netelenbos et al., 2003) and LFA-1 (lymphocyte function associated antigen-1), as well as by other cell adhesion molecules involved in CXCL12 triggered proadhesive interactions in T lymphocytes (Wu et al., 2012).

Regulation of integrin activity maintains the ability of lymphocytes to adhere quickly at sites of infection or inflammation (Wu et al., 2012). Indeed, quiescent type B NSCs are the only cell type that do not display chemotaxis toward CXCL12 or endothelial cell-conditioned medium. However, activated B cells remain in close proximity to blood vessels in the SVZ, and particularly C cells, while type A cells migrate toward the OB (Miller and Gauthier-Fisher, 2009). In this context, chemokines like IL-8 or CXCL12 induce the recruitment of human NPCs across brain endothelial cells (Weiss et al., 2010). In addition, CXCL16 induces migration and invasion by glial precursor cells via its CXCR6 chemokine receptor (Hattermann et al., 2008).

Both ependymal and vascular cells provide important factors for NPC regulation. Noggin (expressed by ependymal cells) induces neurogenesis (Lim et al., 2000) and PDGF (secreted by both ependymal and blood vessels) supports self-renewal (Ramirez-Castillejo et al., 2006). Interestingly, only activated type B and type C cells that are dividing are enriched near blood vessel surfaces (Tavazoie et al., 2008). In fact, the ependymal niche harbors quiescent stem cells, while the vascular niche regulates the transit-amplifying type C cells and type A neuroblasts, which are more strongly attracted to endothelium-derived factors than are quiescent stem cells (Fig. 4)

On the other hand, CXCL12 stimulates type A cells in the SVZ to move toward blood vessels and these type A cells are not normally as close to the vascular surface as activated type B and type C cells. Although type A cells are chemically attracted to endothelial factors, their migratory capacity is less effectively blocked by AMD3100 (a CXCR4 antagonist), suggesting that additional chemoattractant(s) are required for NSC homing to endothelial cells in the SVZ (Miller and Gauthier-Fisher, 2012; Tavazoie et al., 2008). Moreover, CXCL12 upregulates alpha 6 integrin expression on activated type B and type C cells, albeit less so on type A cells. These differential effects on type A, B or C cells may explain how stem cell trafficking of NPCs toward blood vessels is mediated through an CXCL12 gradient. Thus, certain concentrations of CXCL12 could promote type A egression and migration from the vascular niche toward the OB (Snapyan et al., 2009). In this respect, it is important to elucidate how CXCL12 stimulates CXCR4 signaling pathways and NPC migration, issues that are discussed below.

Which Signaling Pathways are Involved in CXCL12 Proliferative Effects in NPC?

The coupling of CXCR4 to different intracellular pathways depends on its activation by its ligand CXCL12 (Khan et al., 2003). Thus, we will briefly describe the cascades involved in CXCL12-mediated NPC proliferation in vitro (i.e., PI-3 kinase/Akt, JAK/STAT pathways, or FOXO-3 activation; Fig. 5).

CXCL12 induces NPC migration through Akt-1 and FOXO3a phosphorylation

It is known that the PI3K/Akt-1 pathway contributes to the proliferation or self-renewal of embryonic stem cells (Paling et al., 2004) and CXCR4 activation regulates second messenger activity through Gi-Go GTP-binding proteins, since PTX (an inhibitor of G proteins) decreased CXCL12-induced NPC proliferation in vitro (Wu et al., 2004). It has been shown that the CXCR4/G protein/PI3K-Akt pathways are responsible for CXCL12-mediated NPC proliferation (Fig. 5), through the phosphorylation of Akt-1 and FOXO3a (Wu et al., 2009; Yumei et al., 2009). Several studies in vitro reported that CXCR4 activation by CXCL12 induces neuronal survival through Akt phosphorylation (activation) and that this can also regulate cell-cycle proteins in post-mitotic neurons (e.g., Retinoblastoma; Rb: Khan et al., 2003, 2008). Akt-1 (a serine/threonine kinase) is a downstream target of PI3K, a kinase known to regulate the survival and proliferation of various cell types, including NPCs (Nakamura et al., 2000; Chang et al., 2003; Brunet et al., 2009). The transcription factor FOXO3a (a downstream target of Akt-1) is directly associated with CXCL12 mediated human NPC proliferation. FOXO3a is one of the FOXO subclass of Forkhead transcription factors (Forkhead box, class O: Birkenkamp et al., 2007) and CXCL12 increases the phosphorylation of Akt-1 and FOXO3a (Wu et al., 2009). As a major substrate of Akt-1, FOXO3a plays a critical role in coordinating cell survival or cell death reponses (Nakamura et al., 2000; Birkenkamp et al., 2007). Thus, one way in which Akt-1 may promote cell survival and proliferation is through FOXO3a phosphorylation (Yang et al., 2008b). CXCR4 antagonist (T140) or inhibitors for G proteins (pertussis toxin, PTX) and PI3K (LY294002) abolished CXCL12-mediated NPC proliferation and phosphorylation of Akt-1 and FOXO3a (Wu et al., 2004, 2009). In conclusion, CXCR4 activation by CXCL12 is coupled to G proteins and p-Akt regulates the proliferative effects of CXCL12 on NPCs in vitro (Fig. 5).

The role of PI3K (p110α and p110β catalytic subunits) in NPC migration via CXCR4/CXCL12 signaling

The two catalytic subunits of PI3K, p110α and p110β, are both activated by EGF (epidermal growth factor) CXCL12 in vitro, and the β isoform of PI3K is responsible for NPC movement toward chemoattractants. PI3K (p110β) is activated by CXCL12 in NPCs and its activity is necessary for immature interneuron migration to the cerebral cortex. However, p110β was not necessary for pyramidal neuron migration, suggesting that the dependence of migration on p110β is cell type and/or chemoattractant dependent in vivo (Holgado et al., 2013).

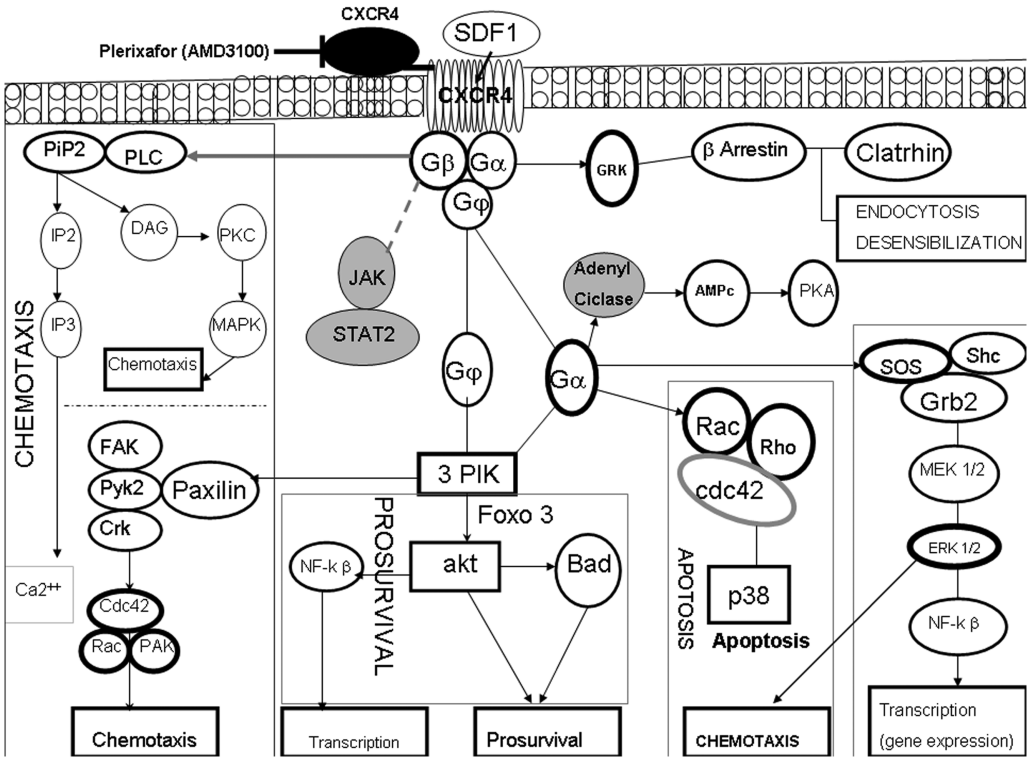

Fig. 5. CXCR4 signaling pathways. CXCR4 induces chemotaxis via Cdc42/Rac or p-ERK 1/2 cascade (right part). Foxo3a and akt phosphorylation promotes survival in NPC bearing CXCR4 chemokine receptor. CXCL12 plays an essential role in modulating axonal responsiveness to several guidance cues through a cyclic nucleotide-dependent signaling pathway (AMPc). Chemokines also mediates chemotaxis via STAT-2/JAK cascade. Clatrin mediates endocytoses (CXCR4+ cells). AMD3100 (a CXCR4 chemokine blocker) blocks CXCL12-induced migration in NPC.

CXCL12 and JAK/STAT or FAK signaling in NPCs

NPCs respond to CXCL12 by activating the JAK (Janus kinases), PI3K and ERK-1/2 pathways, all signaling cascades associated to CXCR4 in cells of the immune system but also, in NPCs in vitro (Vila-Coro et al., 1999; Balabanian et al., 2005; Schabath et al., 2006; Guillermet-Guibert et al., 2008; Fig. 5). Jaks are a small family of cytoplasmic tyrosine kinases, critical for signaling by Type I and II cytokine receptors. The JAK/STAT pathway is another pathway activated by CXCL12 in NPCs in vitro (Holgado et al., 2013; Fig. 5) and NPC proliferation and differentiation are differentially regulated by the Jak pathway (Jin et al., 2005, 2006). CXCL12 induced JAK2 activation and STAT5b association to CXCR4. CXCL12-induced NPC migration is blocked by the JAK2 Inhibitor II or the pan-JAK inhibitor (AG490), as reported for T cells (Soriano et al., 2003). In fact, Jak2 regulates NPC proliferation and maintenance, whereas silencing of JAK3 signaling is essential for NPC differentiation into neurons and oligodendrocytes (Kim et al., 2007, 2010). Moreover, STAT3 activation in NPCs leads to astrogliogenesis (Peng et al., 2012; Chen et al., 2013) and indeed, after CXCL12 binding, JAK2 and JAK3 associate with CXCR4 and are activated (Vila-Coro et al., 1999). Activation of the JAK/STAT pathway by other chemokines has been described, including CCR2 (Mellado et al., 1998), CCR7 (Mellado et al., 2003; Stein et al., 2003) CCR5 (Wong and Fish, 1998; Wong and Korz, 2008) and CXCR4 (Vila-Coro et al., 1999).

Although the JAK/STAT pathway was activated following CXCL12 stimulation of NPCs, JAK activity was not necessary for NPC migration in vitro. Interestingly, JAK2 or JAK3 deficiency does not alter the CXCL12 responses in immune cells (Moriguchi et al., 2005). It has also been suggested that JAK is necessary for CXCL12-mediated STAT recruitment (Ahr et al., 2005). Interestingly, CXCL12 might require the JAK/STAT pathway to trigger neural precursor differentiation induced by IL-6 (Miller and Gauthier, 2007).

ERK-1/2 is another cascade involved in cell migration (Delgado-Martin et al., 2011), connecting the PI3K and MAPK signaling pathways (Lopez-Ilasaca et al., 1997; Bondeva et al., 1998; Gong et al., 2006). ERK-1/2 activation occurs in NPCs treated with TGX-221 in vitro (a p110β inhibitor), suggesting that some crosstalk could exist between these two signaling cascades. In fact, CXCL12-mediated NPC migration decreased after treatment with a specific ERK-1/2 pathway inhibitor, while p110β knockdown blocked CXCL12-induced migration (Holgado et al., 2013). Collectively, these findings indicate that several signaling cascades are involved in the influence of CXCL12 on NPC migration (CXCR4+; Khan et al., 2003; Peng et al., 2004; Fig. 5).

Another cue regulating NPC migration is the homing cascade that determines cell adhesion to brain endothelial cells and transendothelial migration for cell repair (Cui et al., 2007). In this context, metalloproteases (MPP2/9) regulate the trafficking of stem cells (Son et al., 2006). Since the CXCR4/CXCL12 axis mediates active MMP9 and MMP2 secretion in different cell types (Yu et al., 2003; Chu et al., 2007), the chemotaxis seems to be regulated MMP and CXCR4 in vitro (Cui et al., 2007). Accordingly, we must consider how MPP2/9 activation contributes to the regulation of chemokine activity (Mastroianni et al., 2011).

Does Chemokine and Metalloprotease Activity Regulate NPC Migration Toward Damaged Areas of the CNS?

MMPs are a family of metalloendopeptidases that cleave the protein components of the extracellular matrix (ECM) under pathological conditions (Mastroianni and Liuzii, 2007). However, these proteins can also promote tissue repair, remodeling or neurogenesis (Canete-Soler et al., 1995a,b). MMPs are members of the Zn-dependent endopeptidase family, and their expression is transcriptionally controlled by proinflammatory cytokines (cytokines or chemokines), growth factors, hormones, and cell–cell and cell–matrix interactions (Van den Steen et al., 2002; Nagase, 1997). It is noteworthy that MMP-2 activation cleaves CXCL12 into a neurotoxic isoform (the truncated SDF-1 ($_{5–67}$) that reduces NPC proliferation (Zhang et al., 2003; Barkho et al., 2008; Lum et al., 2009; Peng et al., 2013; Fig. 2). CXCL12 induces CXCR4 activation and promotes NPC migration by activating ERK1/2 and Akt-1, decreasing cAMP levels (Peng et al., 2013; Holgado et al., 2013). However, its SDF-1 ($_{5–67}$) truncated form (generated by metalloprotease MMP2/9) fails to induce NPC migration and it does not activate these signaling pathways (Peng et al., 2013). Interestingly, activation of CXCR4 by CXCL12 depends on two domains located at the N-terminal of this alpha chemokine receptor (PepC-C: KPVSLSYRCPCRFFESHIARA). This synthetic peptide upregulates CXCL12 expression in vivo and in vitro, promote chemotaxis of neuroblasts in vivo, and stimulate chemotaxis and proliferation of CXCR4+ cells in vitro, without affecting NSC fate (Filippo et al., 2013). Thus, post-translational CXCL12 cleavage by MMP-2 generate a neurotoxic SDF-1 ($_{5–67}$) form that could reduce NPC migration and induce neurotoxicity (Peng et al., 2000, 2012; Zhang et al., 2003). Conversely, the Metalloproteinase 17 (ADAM17), also known as Tumor necrosis factor-α Converting enzyme is primarily involved in CXCL12-induced shedding from neurons in vitro (Simizu et al., 2010). Moreover, CXCL12 can provoke the cleavage of other chemokines, like fractalkine (CX3CL1, a delta chemokine), by enhancing ADAM17 expression in cortical neurons in vitro. Thus, CXCL12 regulates the expression of ADAM17 rather than directly stimulating its enzymatic activity in cortical neurons in vitro suggesting that MMP activation regulates CXCL12 levels in neural cells (Simizu et al., 2010).

How do Metalloproteases Control the Trafficking of Stem Cells Through CXCR4/CXCL12 Chemokines?

Circulating stem cells release factors that enable them to cross the endothelial barrier and home to an organ (e.g., MMP2 or MMP9: Kucia et al., 2006). Several studies have demonstrated that MMPs regulate the chemotaxis of progenitor cells through the CXCR4/CXCL12 axis. In fact, MMPs play a role in the CXCL12/CXCR4-induced chemotaxis of human hematopoietic progenitor cells across subendothelial basement membranes, a process that is blocked by MMP inhibitors (Janowska-Wieczorek et al., 2000). Indeed, the intracerebral injection of recombinant human CXCL12 stimulates the homing of transplanted bone marrow stromal cells (BMSCs) to the site of injection in the brain (Jin et al., 2006). Since CXCL12 enhances the chemotaxis of bone marrow and blood CD34 (+) cells (Mohle et al., 1998), and this chemotaxis can be blocked by inhibitors of MMPs (Lin et al., 2013; Chambon et al., 2013), these findings indicate that the activation of metalloproteases regulates the chemotaxis of progenitor cells via the CXCR4/CXCL12 axis.

Nitric Oxide (NO) and CXCL12 Regulation: A Role in Repair?

NO produced by eNOS (endothelial nitric oxide synthase) plays a role in angiogenesis and vascular remodeling, and eNOS is also essential for the mobilization of stem and progenitor cells (Aicher et al., 2003), as well as promoting neurogenesis/repair in rodent models of stroke (Zhang et al., 2004; Chen et al., 2005). Interestingly, CXCL12-induces chemotaxis in T cells by a mechanism mediated by NO signaling (Aicher et al., 2003). In fact, the CXCL12/CXCR4 axis mediates the DETA-NONOate ([Z]-1-[N-(2-aminoethyl)-N-(2-ammonioethyl) aminio] diazen-1-ium-1,2-diolate) enhancement of BMSCs for CNS repair, along with MMP9, by increasing CXCL12 and Angiopoietin 1 (Ang1) levels in the SVZ: Zacharek et al., 2006, 2007; Cui et al., 2007). This evidence indicates that NO donors significantly enhance CXCL12-induced cell migration in rodent models of cerebral ischemia (Cherla and Ganju, 2001; Ji et al., 2004a; Zhou et al., 2007). Since CXCR4 blockade or MMP inhibition significantly attenuate DETA-NONOate-induced BMSC migration, CXCR4 and MMP appear to fulfill a crucial role of in the control of NPC migration (Ciu et al., 2007). Indeed, a higher density of secreted MMP9 was evident in SDS-polyacrylamide gel electrophoresis zymography after DETA-NONOate treatment of synergic BMSCs, suggesting that chemokines and MMPs regulate the chemotaxis of progenitor cells. In consonance with this hypothesis, AMD3100 (a CXCR4 chemokine blocker) or GM6001 (an MMP inhibitor) significantly attenuated DETA-NONOate-induced BMSC adhesion to mouse brain endothelial cells (MBECs) or astrocytes (Ciu et al., 2007).

Erythropoietin (EPO) Regulates CXCR4 (CXCL12) Levels Through Specific Signaling Pathways

This glycoprotein and its cognate receptor, EPOR, offer protection against insults in the CNS, and EPO is another factor that regulates CXCR4/CXCL12 expression (Keswani et al., 2005; Tsai et al., 2006; Liao et al., 2008; Chamorro et al., 2013). Since EPO promotes neurogenesis and can induce neuroblast migration from the SVZ toward the OB after CNS damage (Shingo et al., 2001; Chen et al., 2007; Ransome and Turnley, 2007), it may fulfill a fundamental therapeutic role in cerebral ischemia by regulating CXCR4/CXCL12 levels (Wang et al., 2004; Avasarala and Konduru, 2005; Xiong et al., 2007; Brunner et al., 2009).

Ischemic stroke is an example of a CNS pathology where chemokines promote angiogenesis and NPC recruitment (Amantea et al., 2009; Merino et al., 2011; 2013). Stroke is one of the major causes of disability in adults, and is the result of cerebral artery occlusion and blood-brain barrier dysfunction. During the initial phase of cerebral ischemia, inflammatory responses, gliosis, and microglial overactivation occur, provoking an increase in NO and ROS production that leads to neurodegeneration (Zhang et al., 2001; Itoh et al., 2009; Chaturvedi and Kaczmarek, 2013). In the neurovascular niche, MMPs secreted by endothelial cells can breakdown the tight junctions between astrocytes and the endothelium (Venstrom and Reichardt, 1993; Asahi et al., 2001; Ohab et al., 2006; Reuter et al., 2013).

Interestingly, CXCR4 and MMP9 expression can induce both beneficial (Liu et al., 2012) or detrimental effects in the developing and adult brain (Kim et al., 2006; Liu et al., 2008) or spinal cord (Pannu et al., 2007). Since inflammation is detrimental for neurogenesis (Ekdahl et al., 2003) and IL-8, CCL-2, CCR5, leukotriene B4 -LTB4-, and CXCL1-chemokines or cell adhesion molecules (ICAM, Selectin, CD11/CD18 integrins) induce leukocyte recruitment toward damaged CNS areas (Kim, 1996; Kang et al., 2012; Ma et al., 2012), it is important to elucidate how EPO regulates chemokines to guide NPC migration from the SVZ toward the damaged CNS and promote repair (Bye et al., 2012). This feature might be important from a therapeutic view point because TPA (the recombinant tissue plasminogen activator;

a thrombolytic factor) is currently the only clinical agent approved for stroke therapy (Saver et al., 2013).

It is also crucial to study the pathways by which EPO signaling induces chemokine-dependent NPC migration. In this context, NSCs respond to injury by secreting CXCR4/CXCL12, and the cytokines IL-1 Beta, IL-6, TNF-α, IL-4, and IL-10 (Filippo et al., 2013). Cytokine-mediated deployment of CXCL12 induces revascularization through the recruitment of CXCR4+ hemangiocytes (Jin et al., 2006). Since rhEPO-activated endothelial cells enhance NPC migration by secreting MMP2 and MMP9, and by PI3K/Akt activation in vitro, Akt could mediate EPO-induced neuroprotection following insult. However, EPO also induces ERK1/2 signaling, as well as MMP2 and MMP9 secretion (Wang et al., 2006). Since rhEPO-treated MBEC supernatants (conditioned medium) promote the migration of NPCs, an effect that is abolished by MMP inhibitors, EPO might also regulate NPC migration (Asahi et al., 2001; Wang et al., 2004, 2008). Moreover, EPO induces the phosphorylation of FOXO3a via the PI3K/Akt cascade and it leads to the proteolysis that retains it in the cytoplasm by binding to 14-3-3 protein (Chong and Maiese, 2007). It is noteworthy that the protection mediated by EPO against insults in vitro occurs through 3 PI-kinase/Akt activation and NO release. NO generated by nNOS also triggers the release of EPO following insult, and this is prevented by (TRIM) a specific neuronal nNOS inhibitor in vitro (Keswani et al., 2004). In fact, the beneficial effects of rhEPO on post-ischemic progenitor migration are potentially mediated via MPP2 and/or MPP9 secretion, as well as by the phosphoinositol-3-kinase/Akt1 (Cai and Semenza, 2004; Fig. 2) and ERK1/2 signaling pathways (Wang et al., 2006). However, PI3K/Akt and the ERK1/2 inhibitors attenuated the rhEPO-induced MMP2 and MMP9, which suppressed NPC migration promoted by the rhEPO-activated MBECs (Wang et al., 2006). Therefore, EPO-induced NPC migration was dependent on MMPs in endothelial cells (Wang et al., 2006). The reparative role of EPO is consistent with the reported neurite elongation and neuroprotective role induced by peripheral administration of EPO (Pankratova et al., 2012), which promotes neurogenesis, oligodendrogenesis and neurovascular remodeling following traumatic brain injury, and that has a favorable functional outcome in rats (for review, Brettschneider et al., 2006; Kadota et al., 2009). However, there are concerns about the potential clinical use of EPO as it increases hematocrit at the doses required for neurogenesis in rodent models (5000 U/kg), although this adverse effect was abolished by its Carbamylated EPO derivate, which promotes proliferation in the SVZ/dentate gyrus and the neuronal differentiation of adult NPCs (Wang et al., 2006; Leconte et al., 2011), as well as SVZ-derived oligodendrogenesis (Kako et al., 2012). Interestingly, in cerebral models of ischemia enhanced homing of bone marrow-derived progenitor cells through the CXCR4/CXCL12 axis was induced by the neuroprotectant cerebrolysin in cardiomyocytes (Brunner et al., 2009) and neuronal cells in vivo and in vitro (Merino et al., 2009). Since Increased Sca-1(+) and CXCR4(+) homing, and BMSC mobilization, were directed toward an CXCL12 gradient in the ischemic myocardium, these findings would support the notion that EPO promotes protective effects via CXCR4/CXCL12 chemokines (Brunner et al., 2009; Gao et al., 2012).

How Differential CXCL12 Binding via CXCR4 and CXCR7 Regulates NPC Migration/How Does CXCR4-CXCR7 Crosstalk Regulate NPC Migration?

The expression of different chemokine receptors on the same cell can lead to the formation of heterodimers that may enhance or reduce the effects of the chemokines (Percherancier et al., 2005). CXCR7 (RDC1) is the second receptor for CXCL12, a receptor that fails to couple to classic G-protein signaling pathways activated by chemokines (Ehrlich et al., 2013). However, it remains unclear how CXCR7 acts as a scavenger receptor to reduce the availability of CXCL12 for CXCR4 or CXCR7 signaling in NPCs (Boldajipour et al., 2008; Zhu et al., 2012). The chemoattractant properties of NPCs from the SVZ vary in function of the CXCL12 concentration. In fact, CXCL12 has an approximately 10-fold higher affinity for CXCR7 than for CXCR4 (Bakondi et al., 2011; Costantini et al., 2013) and, while CXCR7 regulates the responses to CXCL12 in culture cells, CXCR4 can form heterodimers with CXCR7 (Levoye et al., 2009). CXCR7 is a second and de-orphanized CXCL12 receptor that mediates the anti-apoptotic signaling effects of CXCL12 (Kalatskaya et al., 2009; Sánchez-Martín et al., 2013). In this way, CXCL12 can signal through CXCR7 in large populations of SVZ NPCs that express both these alpha chemokine receptors (Zhu et al., 2012). Indeed, CXCL12 secreted by human CD133-derived multipotent stromal cells promotes NPC survival by activating CXCR7 (Bakondi et al., 2012).

Thus, the existence of a balance between CXCR dimers and monomers at the membrane could explain why the CXCL12 axis promotes NPC or neuronal migration (Costantini et al., 2013). CXCR7 is expressed by neurons, astroglia and vascular cells in the forebrain, suggesting that CXCL12 may signal through CXCR7 in large populations of neural cells (Schönemeier et al., 2008). CXCR7 expression was found to be regulated by the membrane level of CXCR4 (Wang et al., 2008), although activated chemokine receptors are desensitized (Lagane et al., 2005, 2008) and internalized before they are subsequently degraded in the endosome or are recycled back to the cell surface (Kucia et al., 2005a,b). Most CXCR7 receptors are found in early endosomes (Wysoczynski et al., 2005; Hartmann et al., 2008) and thus, the surface expression of this chemokine appears to be regulated at the translational level by modulating its intracellular transport and incorporation into the membrane (at the post-translational level: Sánchez-Martín et al., 2013). Ubiquitination may also regulate CXCR7 trafficking to and from the plasma membrane since CXCR7 is reversibly de-ubiquitinated upon CXCL12 recombinant exposure, and it can even be modulated by lipid rafts (Merixell Canals et al., 2012). Since CXCR7 is expressed at low levels in normal cells and CXCL11 (the ligand for CXCR7) binds to CXCR7 but does not activate GPCR-mediated downstream pathways (Balabanian et al., 2011), the interplay between CXCR4 and CXCR7 might affect the CXCR available at the membrane (Balabanian et al., 2005; Ehrlich et al., 2013). Thus, the balance between CXCR4/CXCR7 could determine the effects of CXCL12 on NPC proliferation after CXCL12 activation (Zhu et al., 2012). In fact, CXCR7 is rapidly transferred to the plasma membrane, and it mediates CXCL12 endocytosis, as well as co-localizing with CXCR4 after exposing NPCs to CXCL12 (Zhu et al., 2012).

CXCL12 protects NPCs from apoptotic challenges through the CXCR7 and CXCR4-mediated endocytotic signaling produced by the activation of ERK1/2 pathways (Zhu et al., 2012). Activation of the CXCL12-CXCR4 pathway is crucial for the migration of hematopoietic stem cells, various immune cells, and malignant tumor cells. However, some differences in their signaling pathways, in particular those involving the expression of the CXCR4 and CXCR7 receptors on the cell surface, could explain the differential influence of CXCL12. While CXCR4 has one classical ligand, CXCL12, CXCR7 responds to both CXCL12 or Interferon-inducible T-cell alpha chemoattractant chemokine I-TAC (C-X-C motif) ligand, CXCL11. Thus, unlike CXCR4, CXCR7 competes with CXCL12 and CXCL11 (Burns et al., 2006), and therefore, CXCL12-mediated responses could potentially be modulated by CXCL11 (Hartman et al., 2008). CXCL11 is also called

Interferon-gamma-inducible protein 9 (IP-9) that is chemotactic for activated T cells. This chemokine elicits its effects on its target cells by interacting with the cell surface chemokine receptor CXCR3, with a higher affinity than do the other ligands for this receptor, CXCL9 and CXCL10 (Hartmann et al., 2008).

CXCL14, specifically binds to CXCR4 with a high affinity and it inhibits the CXCL12-mediated chemotactic responses of human leukemia-derived cell line/CD34(+) hematopoietic progenitor cells. Thus, CXCL14 functions as a natural inhibitor of CXCL12 (Tanegashima et al., 2013) and along with CXCR7, it may modulate stem cell maintenance and immune responses by regulating the CXCR4/CXCL12 responses (Tanegashima et al., 2013).

Finally, CXCL12 can be regulated by hypoxia (Schioppa et al., 2003), and the level of CXCL12 expression and its binding affinity to particular receptors may decide the degree to which the CXCL12/CXCR4 axis or the CXCL12/CXCR7 system influences NPC proliferation (Virgintino et al., 2013). In this context, the responsiveness of CXCR4 to the CXCL12 gradient may be positively modulated or primed by several small molecules involved in inflammation, such as C3 complement cleavage fragments (Ratajczak et al., 2006; Wysoczynski et al., 2007). The molecular explanation for this phenomenon is based on the observation that C3 cleavage fragments enhance the incorporation of CXCR4 into membrane lipid rafts (Wysoczynski et al., 2005), thereby inducing dimerization and promoting the association between CXCR4 and downstream signaling molecules (Wysoczynski et al., 2007). Interestingly, high CXCL12 and C3 cleavage fragments levels in damaged tissues induce a chemoattractant gradient, which is responsible for CXCR4+ stem cell circulation (Wysoczynski et al., 2007). Indeed, the N-terminal end of CXCL12 appears to be responsible for a positive feedback loop that maintains a CXCL12 gradient that attracts neuroblasts from the SVZ into an injury site (Filippo et al., 2013).

Effects of Cytokines on Chemokine Release by NPCs

Cytokines and chemokines have been shown to alter NSC self-renewal and progenitor cell differentiation, which is probably mediated by JAK/STAT signaling and transcriptional activation (Vitkovic et al., 2000; Hiroi and Ohmori, 2003; Das and Basu, 2008; Islam et al., 2009a). Soluble IL-6R (sIL-6R) binds IL-6 and promotes trans-signaling (Taga and Kishimoto, 1997; Jones, 2013). IL-6 also induces differentiation of cortical precursor cells into oligodendrocytes and can activate adult astrocytes (Kahn and De Vellis, 1994). IL-6 induces the differentiation of neural stem cells (NSCs) specifically into glutamate-responsive neurons and two morphological astroglia cell types. In fact, IL-6-activated neurogenesis is induced by the MAPK/CREB (mitogen-activated protein kinase/cAMP response element-binding protein) cascade (Islam et al., 2009a,b; Peng et al., 2011). However, astrocyte differentiation is dependent on IL-6 family cytokine-mediated STAT3 (signal transducers and activators of transcription protein-3) activation (Taga and Kishimoto 1997; Taga and Fukuda, 2005).

Treatment of SVZ-derived NPCs with IFN γ and TNF-alpha (alone or in combination) augmented CXCL1, CXCL9 and CCL2 chemokines but downregulated CCL19 (Turbic et al., 2011). Neuronal differentiation was promoted by CXCL9, CCL2, and CCL21, although astrocyte and total oligodendrocyte differentiation was not affected. Conversely, IFN γ, CXCL1, CXCL9, and CCL2 promoted oligodendrocyte maturation (Hiroi and Ohmori, 2003; Owens et al., 2005; Suyama et al., 2005; Lum et al., 2009; Conductier et al., 2010; Turbic et al. 2011) and TNF-alpha also increased CXCR4 and CCR5 expression by astrocytes (Croitoru-Lamoury et al., 2003). In addition, CCR7 was overexpressed in inflammatory conditions (Gomez-Nicola et al., 2010) while chronic exposure to LIF or CNTF altered the formation of NSC progeny and promoted NSC self-renewal, events inhibited by leptin (Nakai-Futatsugi and Niwa, 2013).

Chemokine/Cytokine	Effect on neural precursor cells
IFN-γ	Reduces NSC proliferation and survival, promotes differentiation and neurite outgrowth (Wong et al., 2004; Bonaguidi et al., 2005; Song et al., 2005; Lum et al., 2009)
IL-4	Increases oligodendrocyte precursors (Suyama et al., 2005; Butovsky et al., 2006; Guan et al., 2008; Lum et al., 2009)
TNF-α	Inhibits neural progenitor differentiation (Croitoru-Lamoury et al., 2003; Belmadani et al., 2005)
Leptin	Inhibits neural progenitors differentiation (Nakai-Futatsugi and Niwa, 2013)
IL-6/LIF	Induces NSC self-renewal, as well as differentiation into glutamatergic neurons or oligodendrocytes (Bonaguidi et al., 2005; Bauer and Patterson, 2006; Butovsky et al., 2006; Oshima et al., 2007; Guan et al., 2008 Covey and Levison, 2008)
Leptin/MCP-1	Affects oligodendroglial growth in the cortex (Udagawa et al., 2006) and acts as a chemotactic factor for neural precursors (Widera et al., 2004)
CCL2 = MCP-1	Promotes neuronal differentiation of SVZ neural progenitors (Edman et al., 2008)
CXCL12 (SDF-1 alpha)	Chemotactic factor that also promotes the survival and proliferation of adult NSCs, and that induces proliferation through EGF activation in NPCs (Zhu et al., 2012). CXCL12 mediates interactions between the endothelium and glioblastoma (Rao et al., 2012)
CNTF	Promotes neurogenesis and stem cell self-renewal (Shimazaki et al., 2001)
CXCL13/IL-8	Chemotaxis of endothelial cells (Weiss et al., 2010).
GRO α	Regulates human embryonic stem cell self-renewal and/or adoption of a neuronal fate. Differentiation (Krtolica et al., 2011)

Chemokines and Cell Therapy in CNS Disorders

Hypoxic preconditioning of transplanted cells induces neurogenesis following cerebral ischemia. A number of engrafted-BMSCs induce chemotactic and trophic effects CXCL12 dependent levels for cell repair (Kucia et al., 2006; Brunner et al., 2009; Weiss et al., 2012). There is a connection between fibroblast growth factor receptor 1 (FGFR-1) activation and macrophage recruitment, which is dependent on CX3CL1 levels (Reed et al., 2012). In fact, macrophages promote fibroblast growth factor receptors (FGFR)-driven tumor cell migration and invasion in a CXCR2-dependent manner (Bohrer and Schwertfeger, 2012). However, FGF has also been shown to have a protective effect against insults by exerting differential effects on neurons and glial cells. This suggests that EGF/FGF can also regulate NPC proliferation following insult, acting through regulatory chemokines (Sanders et al., 2000; Hadjipanayi et al., 2012; Itkin et al., 2012).

Stem cells obtained from periodontal cells can respond to chemokines and 90% of periodontal cells can undergo neuronal differentiation, making them an accessible source of autologous human adult SCs and highlighting their potential for preventing CNS disorders (Widera et al., 2007). Transplantation of BMSCs may be a new approach for brain repair although their clinical use and the results of engraftment are still limited (Dezawa et al., 2005; Kaplan et al., 2007). Chemokines can direct BMSC migration toward damaged areas through chemotactic gradients and, since efficient transfection induces CXCR4 overexpression, BMSCs migrate rapidly toward

CXCL12 (Jin et al., 2006). The combined use of hematopoietic progenitor cells mobilized from bone marrow by granulocyte colony stimulating factor (GCSF) and AMD3100 enhances chemotaxis in mouse models of Alzheimer's disease (Shin et al., 2011). Thus, further studies should assess how chemokines contribute to the homing and migration of normal NPCs within the vascular niche so that this approach can be used in the context of neurodegenerative diseases. The neuroimmune interactions based on activation of the CXCR4/CXCL12 cascade could enhance NPC migration in experimental models of CNS disease, thereby preventing cell death in rodent models of inflammatory or CNS disease, and potentially opening up the possibility of developing new therapies for cell repair (Whitney et al., 2009; Li et al., 2012).

Conclusion and Concluding Remarks

This review presents evidence showing that CXCR4/CXCL12 signaling contributes to NPC migration to areas of CNS damage. The homing cascade that drives cell adhesion to brain endothelial cells and transendothelial migration is important for cell repair (Cui et al., 2007). NPCs in the adult SVZ are associated with the ependymal and vasculature niches that regulate stem cell self-renewal and differentiation. There are several cell types in the SVZ, from activated Type B stem cells to the transit-amplifying type C cells that express EGFR (Abhold et al., 2012) and these are most strongly associated with vascular cells (Miller and Gauthier-Fisher, 2009).

Clearly, much remains to be learnt about how CXCR4/CXCR7 activity controls NPC recruitment to damaged areas of the CNS. However, some studies have shown that classic signaling pathways are involved in neuronal migration, particularly since CXCL12 binding to CXCR4 can mediate G_i activation and induce intracellular signaling in NPCs (van Biesen et al., 1996; Bajetto et al., 1999). Consequently, the activation of 3 PI-kinase/Akt by CXCL12 mediates NPC proliferation (CXCR4+) (Ni et al., 2004), and regulates Akt-1 and FOXO3a phosphorylation (Wu et al., 2009; Holgado et al., 2013). The JAK/STAT or ERK1/2 cascades mediated CXCL12 proliferative effects in NPCs in vitro, along with other signaling pathways.

NO, EPO and metalloprotease activity (MMP2/9 or ADAM17), or CXCL12 availability, regulate CXCR4/CXCR7 chemokine function in NPCs, since CXCR7 expression was found to be regulated by the membrane levels of CXCR4 (Wang et al., 2008). On the other hand, EPO induces NPC migration via the CXCR4/CXCL12 axis, while the NO donor DETA-NONOate promotes SVZ neuroblast cell migration through CXCL12 and Ang1 in the SVZ, supporting their role in CNS repair (Cui et al., 2007). In addition, metalloproteases control stem cells trafficking (Son et al., 2006), since MMP-2 regulates chemotaxis through CXCL12 given that MMP-2 activation cleaves CXCL12 into the truncated CXCL12 (SDF1 alha) ($_{1-56}$) neurotoxic form that impedes progenitor proliferation and migration.

Collectively, these findings support the notion that CXCR4/CXCL12 signaling drives NPC migration to initiate endogenous stem cell-based tissue repair and to regulate the capacity to recruit new neuroblasts from the SVZ/RMS toward damaged areas of the CNS. In this context, CXCL12 can provide a bidirectional signal acting, as a chemoattractant or as an inducer of NPC migration, depending on its concentration. Consequently, understanding the signaling pathways downstream of CXCR4 will be crucial to elucidating how neuroprotectants prevent cell death in the CNS. In this context, NO, MPP2/9, and CXCL12 availability are key factors that regulate homing and repair responses in damaged tissues. Thus, CXCR4 activation by neuroprotectants or new NO donors may possibly prevent CNS damage. However, the carbamylated derivative erythropoietin (cEpo) offers hematopoietic tissue protection without an increase in hematocrit, and its clinical efficacy in inducing the homing of progenitor cells via the CXCR-4/CXCL12 axis remains to be confirmed.

Since metalloprotease activation can be induced in CNS pathologies but may also contribute to neurogenesis, inhibitors of MMPs could regulate the shedding of chemokines. In fact, MMP-2, ADAM17, and ADAM 10 can cleave CXCL12 into a neurotoxic form. Consequently, the use of inhibitors of sheddases and MMP blockers could blunt the inflammatory responses mediated by chemokines and cytokines in the acute phase of cell death. However, the use of MMP 2/9 inhibitors is likely to be less useful in promoting cell repair and axonal regeneration. Further studies will be necessary to clarify the possible therapeutic influence of MMP inhibitors on chemokine levels in neurodegenerative diseases

In conclusion, the CXCR4/CXCL12 axis emerges as a target for neuroprotectants in CNS pathologies.

This review has attempted to provide an update on the neuroimmune interactions by which chemokines regulate NPC migration. Finally, CXCL12 based therapy could stimulate neuroblast recruitment and enhance survival of new formed neurons. Thus, neuroprotectants that activate CXCR4 signaling could possibly prevent apoptosis and induce repair in animal models of HIV-1 neuropathogenesis, multiple sclerosis, cerebral ischemia, Alzheimer or trauma, among other pathological situations. Although there is promising data on CXCR4/CXCL12 and CNS repair, further studies will be necessary before translating chemokine studies into clinical therapies. Nevertheless, beneficial clinical effects of AMD3100 (a CXCR4 chemokine blocker) plus GCSF synergic treatment to mobilize stem cell trafficking by CD34+ cells have already been observed in pediatric patients after 2 to 3 cycles of apheresis, without clinical complications (Hong et al., 2012).

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