Concise Review: The Potential of Stromal Cell-Derived Factor 1 and Its Receptors to Promote Stem Cell Functions in Spinal Cord Repair

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Key Words. Stromal derived factor-1 (SDF-1) • Stem/progenitor cell • Spinal cord injury • Somatic cell therapy • Mesenchymal stem cells • Neural stem cell • Umbilical cord blood

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ABSTRACT

Transplanted stem cells provide beneficial effects on regeneration/recovery after spinal cord injury (SCI) by the release of growth-promoting factors, increased tissue preservation, and provision of a permissive environment for axon regeneration. A rise in chemokine stromal cell-derived factor 1 (SDF-1/CXCL12) expression levels in central nervous system (CNS) injury sites has been shown to play a central role in recruiting transplanted stem cells. Although technically more challenging, it has been shown that after SCI few endogenous stem cells are recruited via SDF-1/CXCR4 signaling. Evidence is accumulating that increasing SDF-1 levels at the injury site (e.g., by exogenous application or transfection methods) further enhances stem cell recruitment. Moreover, SDF-1 might, in addition to migration, also influence survival, proliferation, differentiation, and cytokine secretion of stem cells. Here, we discuss the experimental data available on the role of SDF-1 in stem and progenitor cell biology following CNS injury and suggest strategies for how manipulation of the SDF-1 system could facilitate stem cell-based therapeutic approaches in SCI. In addition, we discuss challenges such as how to circumvent off-target effects in order to facilitate the transfer of SDF-1 to the clinic. STEM CELLS TRANSLATIONAL MEDICINE 2012;1:732–739

INTRODUCTION

Stromal cell-derived factor 1 (SDF-1), also known as CXCL12, and its G-protein-coupled receptors CXCR4 and CXCR7 play a critical role in the development of the central nervous system (CNS) and heart, respectively, as their deficiency is lethal during either embryonic or perinatal development [1, 2]. CXCR4- and SDF-1-deficient mice show abnormal development of the dentate gyrus of the hippocampus [3, 4] and the granule cell layer of the cerebellum [1, 5]. In the adult spinal cord, SDF-1 is expressed mainly in the dorsal corticospinal tract and the meninges [6], whereas its receptor CXCR4 is strongly expressed in the ependymal layer of the central canal [6, 7]. After traumatic spinal cord injury (SCI), SDF-1 and CXCR4 expression is upregulated on mRNA and protein level 2 days postoperation (dpo) in a rat model of light and severe thoracic spinal cord contusion. Induced expression levels are also detectable at 42 dpo [8]. The main source of SDF-1 after SCI is most likely reactive astrocytes [8], which also upregulate SDF-1 after stroke [9] and hypoxic-ischemic injury [10]. Cell types secreting SDF-1 and carrying CXCR4 in the context of SCI are shown in Table 1.

STEM CELL TYPES

Established stem cell types that are frequently used in experimental models of spinal cord repair are considered in this review, including embryonic stem cells (ESCs) and somatic stem cells. The latter are found in fetal, neonatal, and mature tissues of different organs and comprise, for example, neural progenitor cells and mesenchymal stem cells. The potential of stem cells to generate various cell types has received great interest for preclinical and clinical investigations to treat and regenerate the injured spinal cord. On the other hand, beneficial effects have been demonstrated without any lineage-specific differentiation or obvious cell replacement. The ability of transplanted stem cells or their derivatives to release growth-promoting factors or modulate the inflammatory response, providing a permissive environment for regenerating axons or neuroprotection, is discussed. Spinal cord injury has a great impact on cell motility of endogenous or transplanted stem cells, which is influenced by several chemoattractants and cell-surface adhesion molecules. The SDF-1/CXCR4 axis plays a critical role for stem cell motility, as well as for stem cell survival and self-renewal,

Table 1. Cell types expressing SDF-1 and CXCR4 in the context of spinal cord injury

Cell types	Expression of SDF-1	Expression of CXCR4
Dorsal corticospinal tract	[6]	[7]
Meninges	[6]	n.d.
Reactive astrocytes	[8–10]	[7]
Monocytes/macrophages	[6, 111]	[6]
Endothelial cells	[82]	n.d.
Endothelial progenitor cells	n.d.	[82]
Pericytes	n.d.	[88, 90]
Radial glia-like cells in the subpial layer of the spinal cord	[8]	[8]
Neural progenitor cells	n.d.	[23–25]
Ependymal layer of the central canal	n.d.	[6, 7]
Oligodendrocyte precursor cells	n.d.	[24]
Mesenchymal stem cells	[43]	[51]
Cancer cells	n.d.	[103, 106]

Numbers in brackets indicate references.
Abbreviations: n.d., not determined; SDF-1, stromal cell-derived factor 1.

which is discussed in detail in this section. Furthermore, recent approaches to manipulating the SDF-1/CXCR4 axis to enhance regeneration after spinal cord injury are discussed (Fig. 1).

Endogenous Spinal Cord Stem Cells

After SCI, endogenous proliferating progenitor cells [11, 12] migrate to the site of injury. It is assumed that neural precursor cells (NPCs) originate from the ependyma of the central canal and the subpial layer in the adult spinal cord [11–14] and differentiate into neural cells after SCI [15–18]. These findings indicate that adult endogenous NPCs might be useful to enhance functional recovery.

As SDF-1 has been shown to be crucial during development of the CNS, it is suggested that the SDF-1/CXCR4 axis might also play a key role in migration of adult endogenous stem cells after SCI [19]. In the adult spinal cord, the chemokine receptor CXCR4 is strongly expressed in the ependymal layer around the central canal from which endogenous stem cells originate [6, 7]. However, the specific function of CXCR4 expression in ependymal cells is still unknown.

In the report by Knerlich-Lukoschus et al. [8] it is shown that radial glia-like cells that appear in the subpial layer express CXCR4 and SDF-1 after SCI. However, although the specific function of SDF-1/CXCR4 in radial glia-like cells after SCI has yet to be defined, the impact on proliferation, survival, and migration to the injury site has been described for neural precursor cells (see below).

Exogenous Stem Cells

Multipotent Neural Lineage Restricted Progenitor Cells

During development of the CNS, CXCR4 is highly expressed in the ventricular zone [20, 21]. Expression of CXCR4 has also been detected in adult neurogenic regions [22], as well as in both human and rodent adult NPCs from different sources in vitro [23–25]. Grafted NPCs invade damaged areas in various lesion paradigms [26, 27], where they promote recovery through either differentiation into neural cells or neuroprotective [27] and neurite growth-promoting [28] functions. ESCs, on the other hand, are mostly transplanted after predifferentiation into highly purified neural cell populations to avoid tumor formation. Transplantation of ESC-derived NPCs into the injured spinal cord (SC) leads to results similar to those described for NPCs [29–31]. Importantly, responsiveness to injury-mediated migratory stimuli is variable between different NPC populations [32]. NPC as well as ESC-derived NPC migration is mediated mainly by CXCR4, as NPCs respond to SDF-1 by migrating in a dose-dependent manner [21, 33–35]. Because of inflammation, transplanted NPCs upregulate both CXCR4 and CXCR7 [34], possibly leading to enhanced migration to the site of injury. In addition to an increased migratory potential, transplantation of NPCs into the subacute SCI seems to be optimal as NPCs show a good survival rate and lead to functional recovery [36]. However, not all migrating NPC populations express CXCR4 as shown for human NPCs derived from fetal brain tissue that have been transplanted into the ischemic rat brain. Here, only subpopulations of the NPCs expressed CXCR4, but all transplanted cells showed extensive migration potency [26]. These data indicate a CXCR4-independent mechanism of migration that might include CC chemokine receptors. CCR2-expressing NPCs are known to respond to sites of inflammation, as NPCs generated from CCR2 knockout mice exhibit only little migration toward inflammatory sites [37]. Furthermore, hepatocyte growth factor (HGF) has been described to regulate neural stem cell migration [38]. After SCI, transplanted NPCs respond with migration to the lesion site and improve locomotor recovery because of differentiation into functional neural cells [36, 39, 40] or because of their supportive properties [28, 41]. It is suggested that the SDF-1/CXCR4 axis is the key player for NPC migration. As SDF-1 enhances NPC proliferation [14, 33, 42] and survival [43], coadministration of SDF-1 might be a possibility to promote the engraftment of transplanted NPCs after SCI resulting in enhanced functional recovery. For ESC-derived NPCs, Hartmann et al. [44] showed that the SDF-1/CXCR4 axis plays a key role in migration after transplantation into mouse hippocampus, which raises the possibility that SDF-1 is also sufficient for targeting grafted ESC-derived NPCs in the injured spinal cord.

Mesenchymal Stem Cells Derived from Bone Marrow or Umbilical Cord Blood

Transplanted mesenchymal stem cells (MSCs) derived from adult bone marrow or umbilical cord blood migrate to the acute or subacute spinal cord lesion site and enhance regeneration [45–47]. Migration of MSCs is under the control of a large range of growth factors, such as HGF [48, 49] and CC and CXC chemokines. SDF-1 induces migration of MSCs in vitro, but with limited effect, as growth factors such as insulin-like growth factor-1 and platelet-derived growth factor-AB are more potent chemoattractants [50, 51]. Blocking of the SDF-1/CXCR12 axis does not inhibit migration completely, indicating that additional molecules regulate MSC migration [52]. Interestingly, migration of MSCs might depend on the inflammatory state as tumor necrosis factor-α and interferon-γ upregulate the expression of CXCR4, which, in turn, leads to increased MSC migration toward SDF-1 [51, 53]. On the other hand, transforming growth factor-β1 (TGF-β1) downregulates the expression of CXCR4 in MSCs, resulting in reduced migration capacity [54]. The incubation of MSCs with SDF-1 leads to an upregulation of proinflammatory cytokines such as interleukin-6 and regeneration-associated molecules such as leukemia inhibitory factor [55], which could have an impact on inflammation and regeneration. Moreover, SDF-1 could promote survival of transplanted MSCs, as pretreatment of MSCs with SDF-1 results in enhanced survival after oxidative stress in vitro and an increased secretion of prosurvival and angiogenesis-promoting factors [56].

In contrast, other authors reported that a population of CD34$^-$ adult bone marrow-derived stem cells do not express
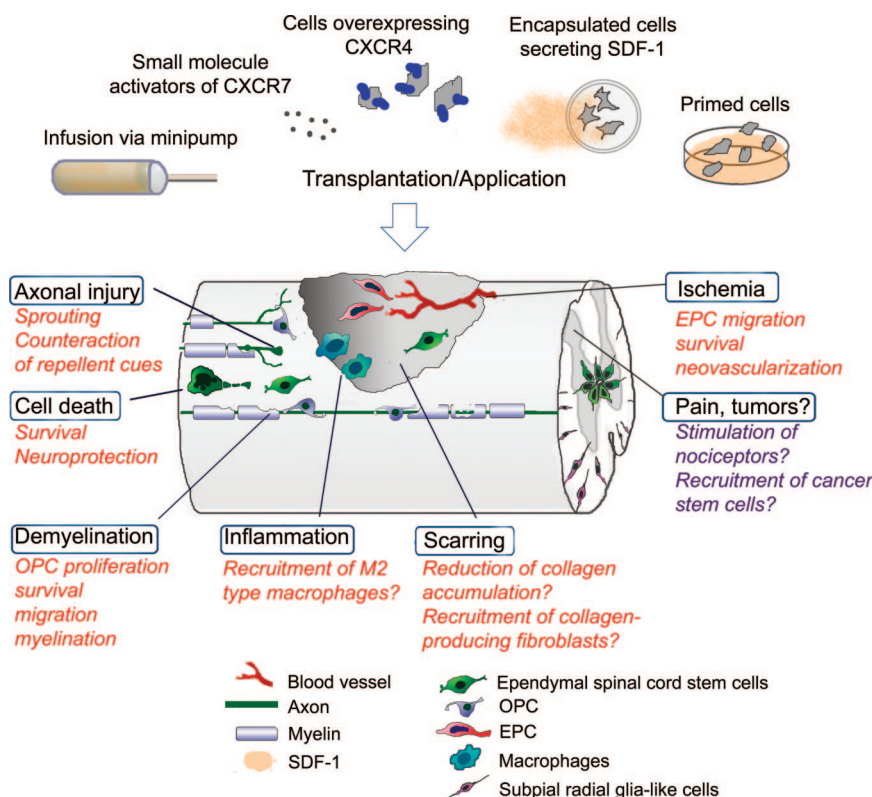
Figure 1. Approaches to promotion of stem and progenitor cell function in spinal cord repair. Endogenous or applied SDF-1 cells enhance the attraction, proliferation, survival, and differentiation of endogenous cells, as well as transplanted stem/progenitor cells (indicated in red), counteracting pathological processes of spinal cord injury. Potential hazards associated with SDF-1 application are indicated in violet. Abbreviations: EPC, endothelial progenitor cell; OPC, oligodendrocyte progenitor cell; SDF-1, stromal cell-derived factor 1.

functional CXCR4 [57], or only a small proportion of MSCs express functionally active CXCR4 [58], which reflects the controversial definition of the MSC. Unfortunately, a specific molecular marker defining MSCs has yet to be found [59]. On the one hand, human umbilical cord blood (hUCB)-derived MSCs migrate toward SDF-1 gradients [60] via Akt, extracellular signal-regulated kinase, and p38 transduction pathways. On the other hand, a subpopulation of stem cells from hUCB (unrestricted somatic stem cells) migrate to SC injury sites mainly driven by HGF gradients [61].

MSCs are known to secrete SDF-1, which has been shown to enhance neurite growth on inhibitory myelin [62] and in the presence of Semaphorin 3A/3C [63] in vitro, as well as axonal sprouting in vivo [7, 62]. In addition, transplanted MSCs could influence glial scarring by stimulating astrocyte proliferation [64], as well as survival of endogenous neural progenitor cells invading the lesion spinal cord, as MSC-secreted SDF-1 protects neural progenitor cells during hypoxia through activation of CXCR7 [43].

EFFECT OF SDF-1 ON REMYELINATION

SCI leads to a dramatic loss of oligodendrocytes, resulting in demyelinated "naked" axons near the lesion that are vulnerable and nonfunctional [65]. Protection of oligodendrocytes from death or promotion of remyelination by endogenous oligodendrocyte precursor cells (OPCs) might be a possibility to enhance functional regeneration. SCI elicits rapid proliferation of OPCs throughout the gray and white matter in both adult rodent and primate spinal cord [65, 66], as well as of ependymal cells sur-

rounding the central canal, which also could give rise to oligodendrocytes after injury [17]. The robust proliferation response that is followed by migration of OPCs into the injury site indicates the presence of local chemoattractants. SDF-1 might function as such a factor in SCI, as the receptor CXCR4 is expressed by primary neonatal OPCs [24] and by neuron glial antigen 2-positive subpial cells (a marker for OPCs) early after SCI [8]. Indeed, it has been shown that SDF-1 increases CXCR4-dependent OPC survival, migration [24], and proliferation in vitro [67]. Moreover, CXCR4-deficient mice show defective OPC survival and ventral to dorsal migration in the embryonic spinal cord. These findings support the idea that manipulation of SDF-1 could speed up recruitment, as well as enhancing OPC survival and proliferation following SCI.

OPC differentiate into oligodendrocytes, which could remyelinate axons starting in the subacute phase at 2 weeks postinjury. Thus, boosting proper differentiation of resident precursor cells would enhance CNS remyelination. Two groups have shown that SDF-1 promotes OPC maturation and myelin production [68, 69]. However, in these studies with different models of demyelination different receptors responsible for OPC maturation have been identified: CXCR4 in cuprizone-mediated demyelination of the corpus callosum [68], and CXCR7 in experimental autoimmune encephalomyelitis (EAE) in the spinal cord [69]. It should be noted that because of the recent discovery of CXCR7 as a second SDF-1/CXCL12 receptor [70], earlier studies have investigated only SDF-1/CXCR4 signaling. Therefore, it still needs to be determined which SDF-1/CXCL12 receptor is required for oligodendrocyte maturation following SCI. If the receptor responsible

for OPC differentiation is CXCR7, then CXCR7-specific small molecule-based activators could promote remyelination without interference with immune cells, which in adult mammals do not express CXCR7 [44, 71].

CONTROVERSIAL FUNCTION OF SDF-1 IN THE WOUND HEALING RESPONSE

A fibrotic glial scar forms during the first week after traumatic SCI and seals the blood-spinal cord barrier. The collagen-rich lesion scar is considered a major impediment for axon regeneration, and several strategies suppressing scar formation have been shown to increase axon regrowth into the lesion site and beyond [72, 73]. Thus far it is not known whether SDF-1 influences scar formation. Intriguingly, SDF-1 was reported to act antifibrotically in the infarcted heart [74], as the adenovirus-mediated transduction of the infarcted heart with SDF-1 in the acute stage led to decreased TGF-β1 expression, which, in turn, led to reduced collagen accumulation in the infarcted area [74]. Similarly, in another study, acute transplantation of lentivirally SDF-1α-infected endothelial progenitor cells revealed a lower collagen content in the infarcted myocardium [75]. On the other hand, SDF-1/CXCR4 signaling has been implicated in promoting migration of activated CD14$^+$ CXCR4$^+$ peripheral blood mononuclear cells to wound sites, where they might differentiate into fibrocytes and myofibroblasts, thus contributing to the development of a hypertrophic scar [76]. In line with this, depletion of SDF-1 in a mouse model of sickle cell disease resulted in a marked reduction of fibrocyte trafficking into the lungs, resulting in reduced lung collagen content and improved lung compliance [77]. Therefore, it still remains to be investigated whether SDF-1 acts antifibrotically or contributes to scar formation in SCI.

NEOVASCULARIZATION

After SCI, endothelial cells and blood vessels degenerate during the first days, exacerbating hemorrhage and tissue ischemia [78]. In addition, SCI leads to breakdown of the blood-spinal cord barrier (BSCB) with the influx of ions, neurotoxic substances, and inflammatory cells, all contributing to secondary damage [79]. A robust angiogenic response is observed 3–14 days after injury [78]. The formation of new vessels to deliver oxygen and nutrients is considered vital for neuronal regeneration and functional recovery, as shown in a number of models of SCI, where the treatments increased blood vessel density [80−82]. The aim of the therapies is to stimulate angiogenesis without excessive vascular permeability and restoration of the BSCB in the subacute phase after SCI. The crucial role of SDF-1/CXCR4 in embryonic vasculogenesis is shown by blood vessel abnormalities manifested in SDF-1a$^{-/-}$ and CXCR4$^{-/-}$ mice [5]. Interestingly, the CXCR7 knockout mouse showed disrupted cardiac development [2], indicating that SDF-1/CXCR7 signaling could play a special role in endothelial biology [83].

Hypoxia induces expression of SDF-1 [84], which is likely one mechanism by which hypoxia drives neovascularization. Indeed, application of SDF-1 promotes neovascularization after traumatic brain injury (TBI) [85], after stroke [86], and in ischemic tissues [87]. After TBI, injection of SDF-1 into the brain penumbra at the acute stage increased the microvessel density around the injured area, whereas application of a SDF-1α neutralizing antibody significantly decreased spontaneous neovascularization [85]. Similarly to TBI, in a stroke model, intracerebral administration of SDF-1 in acute phase increased vascular density and consequently enhanced functional local cerebral blood flow in the penumbra and hippocampus. In both studies, significant improvement of neurological function upon SDF-1 application was found, which might be partially caused by an angiogenic effect [86]. It remains to be studied whether application of SDF-1 into the lesion area could improve microcirculation and restore the BSCB with proper morphology after SCI. In addition, SDF-1 might engage itself in neurovascular niche similarly to brain [88].

The likely mechanism of the SDF-1/CXCR4 axis enhancing neovascularization comprises the attraction of endogenous CXCR4$^+$ endothelial progenitor cells (EPCs) or pericyte progenitors [89] to the injury site. It has been demonstrated that resident microvascular CD133$^+$ pericytes show a corresponding trend with SDF-1 levels following SCI [90]. Additionally, rat MSCs that were engineered to overexpress CXCR4 and intravenously infused were recruited at significantly higher numbers and increased the capillary vascular volume of the peri-infarct area after stroke [91].

STRATEGIES TO MANIPULATE THE SDF-1/CXCR4 AXIS TO ENHANCE RECOVERY AFTER SCI

The SDF-1/CXCR4 axis has not been manipulated in humans after SCI. Moreover, the expression pattern of SDF-1 and CXCR4/CXCR7 has to be analyzed in detail in humans after SCI. However, the SDF-1/CXCR4 axis has been experimentally manipulated in different ways: SDF-1 has been intrathecally infused with minipumps [62] or scaffolds have been transplanted releasing SDF-1 over periods of up to 7 days [92]. Additionally, local transfection with SDF-1 plasmids [93] and transplantation of SDF-1- or CXCR4-overexpressing cells [91] have been used. The latter approach might have advantages as frequently passaged cells downregulate CXCR4 expression [56]. Transplantation of cells constitutively secreting SDF-1 enclosed in microcapsules would be an alternative. Importantly, the short half-life of SDF-1 due to rapid degradation/inactivation by proteases at the injury site and in the blood is even less than half an hour [94]. Therefore, SDF-1 applied in solution should contain a carrier protein to increase its stability. An alternative for SDF-1 would be the newly developed small peptide analogs with improved bioavailability, higher stability, and comparable or even increased functionality [87, 95−97].

On the other hand, strategies enhancing SDF-1/CXCR4 signaling might counteract the limited time of SDF-1 action in tissues. For example, priming of human bone marrow CD34$^+$ stem cells with complement cleavage fragments enhanced their homing in a murine transplant model [98], because cells respond robustly even to very low SDF-1 gradients in the presence of priming factors [99]. Moreover, low levels of TGF-β1 can modulate SDF-1 responsiveness [100]. Interestingly, pretreatment of cells with SDF-1 increases their homing after transplantation as shown, for example, for human cardiac mesoangioblasts transplanted into the heart [101].

Under physiological conditions, SDF-1 readily changes between monomeric and dimeric states that influence its action.

However, there is some discrepancy between published results. It was reported that SDF-1 dimers, which preferentially form at higher concentrations, halt cell migration, whereas monomers promote chemotaxis in vivo [102]. In contrast, Ray et al. [103] found that dimeric SDF-1 more effectively promotes chemotaxis of CXCR4-expressing breast cancer cells. Although CXCR7 preferentially sequestered monomeric SDF-1 from the extracellular space, it had minimal effects on dimeric SDF-1 [103]. Importantly, at high concentrations, SDF-1 repels many CXCR4-expressing cell types [104]. Since SDF-1 increases the vascular permeability, therapeutic dosages of SDF-1 need to be adjusted carefully in clinical applications [86, 105]. Nonetheless, acute intracerebral administration of SDF-1 did not alter physiological parameters such as systemic blood pressure, blood gases, blood glucose, or serum electrolyte levels [86].

Manipulation of the SDF-1/CXCR4 axis could be beneficial for acute or subacute stages as it has an impact on early processes after SCI, such as inflammation and neovascularization, as well as creating an environment for axon regeneration. In fact, most of the stem/progenitor cell transplantations have been conducted in acute or subacute phase of SCI, as the transplanted cells survive best at this stage and transplantation into the chronic SCI does not lead to functional recovery (at least in rodents). In chronic stages, the beneficial effects might be weaker. It is likely that incomplete SCI would profit more than complete regardless of the injury level.

TUMORIGENIC POTENCY AND NEUROPATHIC PAIN

In addition to stem cells, SDF-1 might mobilize transformed stem cells (cancer stem cells) [106]. Most tumors are, indeed, CXCR4^{+} and tend to metastasize to the bones and lymph nodes that highly express SDF-1 in an SDF-1-dependent manner [107]. Although there is no evidence that local application of SDF-1 would increase tumor incidence, systematic evaluation is a basic prerequisite for clinical translation of SDF-1.

SDF-1 could potentially modulate sensitivity following SCI. When injected into the adult rat hind paw, SDF-1 produces dose-dependent tactile allodynia by directly exciting nociceptive dorsal root ganglia neurons that express CXCR4 [108]. Knerlich-Lukoschus et al. [109] reported a correlation between increased SDF-1 immunoreactivity in the dorsal column and dorsal horns with lowering of thermal and mechanical thresholds on spinal cord level L3–L5 at 6 weeks post-SCI, whereas there was no correlation of increased CXCR4 immunoreactivity in the dorsal horns with the nociceptive thresholds [109]. However, in our experiments, we did not observe signs of extra hypersensitivity by postoperative care of rats, which had received SDF-1 infusion for 1 week and were observed for 4 months. Clearly, it should be investigated whether application of SDF-1 into the spinal cord would change nociception following SCI, but application of SDF-1 in a long-term approach to the spinal cord is not likely to be feasible because of potential oncogenic characteristics.

STIMULATION OF THE IMMUNE RESPONSE

SDF-1 was shown to be involved in macrophage infiltration into the spinal cord lesion site, as application of the CXCR4 inhibitor AMD3100 reduced the influx of myeloid cells by 28%–30% [110]. Additionally, Tysseling et al. [6] observed massive infiltration of CXCR4^{+} macrophages in green fluorescence protein-CXCR4 mice following SCI, which also appeared to secrete SDF-1 [6, 111]. None of these studies, however, distinguished among the proinflammatory M1 or anti-inflammatory M2 macrophage subtypes. Importantly, M2 macrophages show expression levels of CXCR4 16 times as high as those of M1 macrophages [112], suggesting a higher responsiveness to SDF-1. If so, infusion of SDF-1 into the acute or subacute injury site might enable selective modulation of inflammatory responses in SCI.

CONCLUSION

SDF-1, which is upregulated at the site of traumatic spinal cord or brain injury, has been shown to be crucial for the recruitment of transplanted stem cells and endogenous progenitor cells to promote functional recovery. It remains to be investigated whether grafting cells in combination with SDF-1 application would result in synergistic promotion of recruitment of both endogenous and transplanted stem/progenitor cells. Furthermore, SDF-1 can directly drive the proliferation, survival, and maturation of OPC and EPCs to promote remyelination and neovascularization, respectively. Moreover, it has been shown that SDF-1 directly stimulates axon growth in vitro and in damaged spinal cord. There is a substantial amount of supporting data about SDF-1 in CNS conditions such as stroke, TBI, and EAE. However, many of the findings remain to be shown in SCI. SDF-1 is more likely to manipulate the SDF-1/CXCR4 axis in acute or subacute stages than in chronic stages, as this manipulation has an impact on early processes after SCI, such as neovascularization and remyelination. Whether SDF-1 application could promote functional recovery in chronic SCI has to be investigated. It is crucial to systematically evaluate potential hazards (neuropathic pain, tumorigenicity) that might go along with long-term application of SDF-1. Nonetheless, tumorigenic potency could be overcome, for example, by transplantation of modified stem cells, overexpressing CXCR4, which were reported showing increased recruitment compared to controls. Only the accomplishment of the crucial studies will allow full assessment of the clinical potential of SDF-1 in SCI.

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AUTHOR CONTRIBUTIONS

A.J.: outline and writing of the manuscript, design of Figure 1; J.S.: outline and writing of the manuscript, improving Figure 1; H.W.M.: editing and final approval of the manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

REFERENCES

1 Zou YR, Kottmann AH, Kuroda M et al. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. Nature 1998;393:595–599.

2 Sierro F, Biben C, Martinez-Munoz L et al. Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7. Proc Natl Acad Sci USA 2007;104:14759–14764.

3 Bagri A, Gurney T, He X et al. The chemokine SDF1 regulates migration of dentate granule cells. Development 2002;129:4249–4260.

4 Lu M, Grove EA, Miller RJ. Abnormal development of the hippocampal dentate gyrus in mice lacking the CXCR4 chemokine receptor. Proc Natl Acad Sci USA 2002;99:7090–7095.

5 Ma Q, Jones D, Borghesani PR et al. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. Proc Natl Acad Sci USA 1998;95:9448–9453.

6 Tysseling VM, Mithal D, Sahni V et al. SDF1 in the dorsal corticospinal tract promotes CXCR4+ cell migration after spinal cord injury. J Neuroinflammation 2011;8:16.

7 Jaerve A, Schiwy N, Schmitz C et al. Differential effect of aging on axon sprouting and regenerative growth in spinal cord injury. Exp Neurol 2011;231:284–294.

8 Knerlich-Lukoschus F, von der Ropp-Brenner B, Lucius R et al. Chemokine expression in the white matter spinal cord precursor niche after force-defined spinal cord contusion injuries in adult rats. Glia 2010;58:916–931.

9 Hill WD, Hess DC, Martin-Studdard A et al. SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: Association with bone marrow cell homing to injury. J Neuropathol Exp Neurol 2004;63:84–96.

10 Miller JT, Bartley JH, Wimborne HJC et al. The neuroblast and angioblast chemotaxic factor SDF-1 (CXCL12) expression is briefly up regulated by reactive astrocytes in brain following neonatal hypoxic-ischemic injury. BMC Neurosci 2005;6:63.

11 Namiki J, Tator CH. Cell proliferation and nestin expression in the ependyma of the adult rat spinal cord after injury. J Neuropathol Exp Neurol 1999;58:489–498.

12 Shibuya S, Miyamoto O, Auer RN et al. Embryonic intermediate filament, nestin, expression following traumatic spinal cord injury in adult rats. Neuroscience 2002;114:905–916.

13 Shibuya S, Miyamoto O, Itano T et al. Temporal progressive antigen expression in radial glia after contusive spinal cord injury in adult rats. Glia 2003;42:172–183.

14 Wu D, Shibuya S, Miyamoto O et al. Increase of NG2-positive cells associated with radial glia following traumatic spinal cord injury in adult rats. J Neurocytol 2005;34:459–469.

15 Dias TB, Yang YJ, Ogai K et al. Notch signaling controls generation of motor neurons in the lesioned spinal cord of adult zebrafish. J Neurosci 2012;32:3245–3252.

16 Mothe AJ, Tator CH. Proliferation, migration, and differentiation of endogenous ependymal region stem/progenitor cells following minimal spinal cord injury in the adult rat. Neuroscience 2005;131:177–187.

17 Meletis K, Barnabe-Heider F, Carlen M et al. Spinal cord injury reveals multilineage differentiation of ependymal cells. PLoS Biol 2008;6:e182.

18 Ke Y, Chi L, Xu R et al. Early response of endogenous adult neural progenitor cells to acute spinal cord injury in mice. STEM CELLS 2006;24:1011–1019.

19 Jaerve A, Bosse F, Muller HW. SDF-1/CXCL12: Its role in spinal cord injury. Int J Biochem Cell Biol 2012;44:452–456.

20 Stumm RK, Zhou C, Ara T et al. CXCR4 regulates interneuron migration in the developing neocortex. J Neurosci 2003;23:5123–5130.

21 Tissir F, Wang C-E, Goffinet AM. Expression of the chemokine receptor Cxcr4 mRNA during mouse brain development. Brain Res Dev Brain Res 2004;149:63–71.

22 Tran PB, Banisadr G, Ren D et al. Chemokine receptor expression by neural progenitor cells in neurogenic regions of mouse brain. J Comp Neurol 2007;500:1007–1033.

23 Tran PB, Ren D, Veldhouse TJ et al. Chemokine receptors are expressed widely by embryonic and adult neural progenitor cells. J Neurosci Res 2004;76:20–34.

24 Dziembowska M, Tham TN, Lau P et al. A role for CXCR4 signaling in survival and migration of neural and oligodendrocyte precursors. Glia 2005;50:258–269.

25 Peng H, Kolb R, Kennedy JE et al. Differential expression of CXCL12 and CXCR4 during human fetal neural progenitor cell differentiation. J Neuroimmune Pharmacol 2007;2:251–258.

26 Kelly S, Bliss TM, Shah AK et al. Transplanted human fetal neural stem cells survive, migrate, and differentiate in ischemic rat cerebral cortex. Proc Natl Acad Sci USA 2004;101:11839–11844.

27 Pluchino S, Zanotti L, Rossi B et al. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. Nature 2005;436:266–271.

28 Lu P, Jones LL, Snyder EY et al. Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. Exp Neurol 2003;181:115–129.

29 McDonald JW, Liu XZ, Qu Y et al. Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. Nat Med 1999;5:1410–1412.

30 Liu S, Qu Y, Stewart TJ et al. Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. Proc Natl Acad Sci USA 2000;97:6126–6131.

31 Nistor GI, Totoiu MO, Haque N et al. Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. Glia 2005;49:385–396.

32 Darsalia V, Kallur T, Kokaia Z. Survival, migration and neuronal differentiation of human fetal striatal and cortical neural stem cells grafted in stroke-damaged rat striatum. Eur J Neurosci 2007;26:605–614.

33 Imitola J, Raddassi K, Park Ki et al. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1alpha/CXC chemokine receptor 4 pathway. Proc Natl Acad Sci USA 2004;101:18117–18122.

34 Carbajal KS, Schaumburg C, Strieter R et al. Migration of engrafted neural stem cells is mediated by CXCL12 signaling through CXCR4 in a viral model of multiple sclerosis. Proc Natl Acad Sci USA 2010;107:11068–11073.

35 Hartman NW, Carpentino JE, LaMonica K et al. CXCL12-mediated guidance of migrating embryonic stem cell-derived neural progenitors transplanted into the hippocampus. PLoS One 2010;5:e15856.

36 Karimi-Abdolrezaee S, Eftekharpour E, Wang J et al. Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. J Neurosci 2006;26:3377–3389.

37 Belmadani A, Tran PB, Ren D et al. Chemokines regulate the migration of neural progenitors to sites of neuroinflammation. J Neurosci 2006;26:3182–3191.

38 Takeuchi H, Natsume A, Wakabayashi T et al. Intravenously transplanted human neural stem cells migrate to the injured spinal cord in adult mice in an SDF-1- and HGF-dependent manner. Neurosci Lett 2007;426:69–74.

39 Cummings BJ, Uchida N, Tamaki SJ et al. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. Proc Natl Acad Sci USA 2005;102:14069–14074.

40 Salazar DL, Uchida N, Hamers FPT et al. Human neural stem cells differentiate and promote locomotor recovery in an early chronic spinal cord injury NOD-scid mouse model. PLoS One 2010;5:e12272.

41 Pallini R, Vitiani LR, Bez A et al. Homologous transplantation of neural stem cells to the injured spinal cord of mice. Neurosurgery 2005;57:1014–1025; discussion 1014–1025.

42 Gong X, He X, Qi L et al. Stromal cell derived factor-1 acutely promotes neural progenitor cell proliferation in vitro by a mechanism involving the ERK1/2 and PI-3K signal pathways. Cell Biol Int 2006;30:466–471.

43 Bakondi B, Shimada IS, Peterson BM et al. SDF-1α secreted by human CD133-derived multipotent stromal cells promotes neural progenitor cell survival through CXCR7. Stem Cells Dev 2011;20:1021–1029.

44 Hartmann TN, Grabovsky V, Pasvolsky R et al. A crosstalk between intracellular CXCR7 and CXCR4 involved in rapid CXCL12-triggered integrin activation but not in chemokine-triggered motility of human T lymphocytes and CD34+ cells. J Leukoc Biol 2008;84:1130–1140.

45 Pal R, Gopinath C, Rao NM et al. Functional recovery after transplantation of bone marrow-derived human mesenchymal stromal cells in a rat model of spinal cord injury. Cytotherapy 2010;12:792–806.

46 Himes BT, Neuhuber B, Coleman C et al. Recovery of function following grafting of human bone marrow-derived stromal cells into the injured spinal cord. Neurorehabil Neural Repair 2006;20:278–296.

47 Čížková D, Rosocha J, Vanický I et al. Transplants of human mesenchymal stem cells improve functional recovery after spinal cord injury in the rat. Cell Mol Neurobiol 2006;26:1167–1180.

48 Neuss S, Becher E, Wöltje M et al. Functional expression of HGF and HGF receptor/c-met in adult human mesenchymal stem cells suggests a role in cell mobilization, tissue repair, and wound healing. Stem Cells 2004;22:405–414.

49 Vogel S, Trapp T, Börger V et al. Hepatocyte growth factor-mediated attraction of mesenchymal stem cells for apoptotic neuronal and cardiomyocytic cells. Cell Mol Life Sci 2010;67:295–303.

50 Ozaki Y, Nishimura M, Sekiya K et al. Comprehensive analysis of chemotactic factors for bone marrow mesenchymal stem cells. Stem Cells Dev 2007;16:119–129.

51 Ponte AL, Marais E, Gallay N et al. The in vitro migration capacity of human bone marrow mesenchymal stem cells: Comparison of chemokine and growth factor chemotactic activities. Stem Cells 2007;25:1737–1745.

52 Abbott JD, Huang Y, Liu D et al. Stromal cell-derived factor-1alpha plays a critical role in stem cell recruitment to the heart after myocardial infarction but is not sufficient to induce homing in the absence of injury. Circulation 2004;110:3300–3305.

53 Hemeda H, Jakob M, Ludwig A-K et al. Interferon-gamma and tumor necrosis factor-alpha differentially affect cytokine expression and migration properties of mesenchymal stem cells. Stem Cells Dev 2010;19:693–706.

54 Wright N, de Lera TL, García-Moruja C et al. Transforming growth factor-beta1 down-regulates expression of chemokine stromal cell-derived factor-1: Functional consequences in cell migration and adhesion. Blood 2003;102:1978–1984.

55 Stich S, Haag M, Häupl T et al. Gene expression profiling of human mesenchymal stem cells chemotactically induced with CXCL12. Cell Tissue Res 2009;336:225–236.

56 Liu X, Duan B, Cheng Z et al. SDF-1/CXCR4 axis modulates bone marrow mesenchymal stem cell apoptosis, migration and cytokine secretion. Protein Cell 2011;2:845–854.

57 Von Lüttichau I, Notohamiprodjo M, Wechselberger A et al. Human adult CD34-progenitor cells functionally express the chemokine receptors CCR1, CCR4, CCR7, CXCR5, and CCR10 but not CXCR4. Stem Cells Dev 2005;14:329–336.

58 Wynn RF, Hart CA, Corradi-Perini C et al. A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 2004;104:2643–2645.

59 Hirvonen T, Suila H, Kotovuori A et al. The i blood group antigen as a marker for umbilical cord blood-derived mesenchymal stem cells. Stem Cells Dev 2012;21:455–464.

60 Ryu CH, Park SA, Kim SM et al. Migration of human umbilical cord blood mesenchymal stem cells mediated by stromal cell-derived factor-1/CXCR4 axis via Akt, ERK, and p38 signal transduction pathways. Biochem Biophys Res Commun 2010;398:105–110.

61 Schira J, Gasis M, Estrada V et al. Significant clinical, neuropathological and behavioural recovery from acute spinal cord trauma by transplantation of a well-defined somatic stem cell from human umbilical cord blood. Brain 2012;135:431–446.

62 Opatz J, Kury P, Schiwy N et al. SDF-1 stimulates neurite growth on inhibitory CNS myelin. Mol Cell Neurosci 2009;40:293–300.

63 Chalasani SH, Sabelko KA, Sunshine MJ et al. A chemokine, SDF-1, reduces the effectiveness of multiple axonal repellents and is required for normal axon pathfinding. J Neurosci 2003;23:1360–1371.

64 Bajetto A, Barbero S, Bonavia R et al. Stromal cell-derived factor-1alpha induces astrocyte proliferation through the activation of extracellular signal-regulated kinases 1/2 pathway. J Neurochem 2001;77:1226–1236.

65 Rabchevsky AG, Sullivan PG, Scheff SW. Temporal-spatial dynamics in oligodendrocyte and glial progenitor cell numbers throughout ventrolateral white matter following contusion spinal cord injury. Glia 2007;55:831–843.

66 Yang H, Lu P, McKay HM et al. Endogenous neurogenesis replaces oligodendrocytes and astrocytes after primate spinal cord injury. J Neurosci 2006;26:2157–2166.

67 Kadi L, Selvaraju R, de Lys P et al. Differential effects of chemokines on oligodendrocyte precursor proliferation and myelin formation in vitro. J Neuroimmunol 2006;174:133–146.

68 Patel JR, McCandless EE, Dorsey D et al. CXCR4 promotes differentiation of oligodendrocyte progenitors and remyelination. Proc Natl Acad Sci USA 2010;107:11062–11067.

69 Göttle P, Kremer D, Jander S et al. Activation of CXCR7 receptor promotes oligodendroglial cell maturation. Ann Neurol 2010;68:915–924.

70 Balabanian K, Lagane B, Infantino S et al. The chemokine SDF-1/CXCL12 binds to and signals through the orphan receptor RDC1 in T lymphocytes. J Biol Chem 2005;280:35760–35766.

71 Berahovich RD, Zabel BA, Penfold ME et al. CXCR7 protein is not expressed on human or mouse leukocytes. J Immunol 2010;185:5130–5139.

72 Klapka N, Hermanns S, Straten G et al. Suppression of fibrous scarring in spinal cord injury of rat promotes long-distance regeneration of corticospinal tract axons, rescue of primary motoneurons in somatosensory cortex and significant functional recovery. Eur J Neurosci 2005;22:3047–3058.

73 Schiwy N, Brazda N, Müller HW. Enhanced regenerative axon growth of multiple fibre populations in traumatic spinal cord injury following scar-suppressing treatment. Eur J Neurosci 2009;30:1544–1553.

74 Tang J, Wang J, Song H et al. Adenovirus-mediated stromal cell-derived factor-1 alpha gene transfer improves cardiac structure and function after experimental myocardial infarction through angiogenic and antifibrotic actions. Mol Biol Rep 2010;37:1957–1969.

75 Schuh A, Kroh A, Konschalla S et al. Myocardial regeneration by transplantation of modified endothelial progenitor cells expressing SDF-1 in a rat model. J Cell Mol Med 2012 (in press).

76 Ding J, Hori K, Zhang R et al. Stromal cell-derived factor 1 (SDF-1) and its receptor CXCR4 in the formation of postburn hypertrophic scar (HTS). Wound Repair Regen 2011;19:568–578.

77 Field JJ, Burdick MD, DeBaun MR et al. The role of fibrocytes in sickle cell lung disease. PLoS One 2012;7:e33702.

78 Casella GT, Bunge MB, Wood PM. Endothelial cell loss is not a major cause of neuronal and glial cell death following contusion injury of the spinal cord. Exp Neurol 2006;202:8–20.

79 Popovich PG, Horner PJ, Mullin BB et al. A quantitative spatial analysis of the blood-spinal cord barrier. I. Permeability changes after experimental spinal contusion injury. Exp Neurol 1996;142:258–275.

80 Zhang Z, Guth L. Experimental spinal cord injury: Wallerian degeneration in the dorsal column is followed by revascularization, glial proliferation, and nerve regeneration. Exp Neurol 1997;147:159–171.

81 Glaser J, Gonzalez R, Perreau VM et al. Neutralization of the chemokine CXCL10 enhances tissue sparing and angiogenesis following spinal cord injury. J Neurosci Res 2004;77:701–708.

82 Kaneko S, Iwanami A, Nakamura M et al. A selective Sema3A inhibitor enhances regenerative responses and functional recovery of the injured spinal cord. Nat Med 2006;12:1380–1389.

83 Yan X, Cai S, Xiong X et al. Chemokine receptor CXCR7 mediates human endothelial progenitor cells survival, angiogenesis, but not proliferation. J Cell Biochem 2012;113:1437–1446.

84 Ceradini DJ, Kulkarni AR, Callaghan MJ et al. Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med 2004;10:858–864.

85 Li S, Wei M, Zhou Z et al. SDF-1alpha induces angiogenesis after traumatic brain injury. Brain Res 2012;1444:76–86.

86 Shyu WC, Lin SZ, Yen PS et al. Stromal cell-derived factor-1 alpha promotes neuroprotection, angiogenesis, and mobilization/homing of bone marrow-derived cells in stroke rats. J Pharmacol Exp Ther 2008;324:834–849.

87 Ziegler M, Elvers M, Baumer Y et al. The bispecific SDF1-GPVI fusion protein preserves myocardial function after transient ischemia in mice. Circulation 2012;125:685–696.

88 Song N, Huang Y, Shi H et al. Overexpression of platelet-derived growth factor-BB increases tumor pericyte content via stromal-derived factor-1alpha/CXCR4 axis. Cancer Res 2009;69:6057–6064.

89 Kokovay E, Goderie S, Wang Y et al. Adult SVZ lineage cells home to and leave the vascular niche via differential responses to SDF1/CXCR4 signaling. Cell Stem Cell 2010;7:163–173.

90 Graumann U, Ritz MF, Rivero BG et al. CD133 expressing pericytes and relationship to SDF-1 and CXCR4 in spinal cord injury. Curr Neurovasc Res 2010;7:144–154.

91 Yu X, Chen D, Zhang Y et al. Overexpression of CXCR4 in mesenchymal stem cells promotes migration, neuroprotection and angiogenesis in a rat model of stroke. J Neurol Sci 2012;316:141–149.

92 Rabbany SY, Pastore J, Yamamoto M et al. Continuous delivery of stromal cell-derived factor-1 from alginate scaffolds accelerates wound healing. Cell Transplant 2010;19:399–408.

93 Kuliszewski MA, Kobulnik J, Lindner JR et al. Vascular gene transfer of SDF-1 promotes endothelial progenitor cell engraftment and enhances angiogenesis in ischemic muscle. Mol Ther 2011;19:895–902.

94 Misra P, Lebeche D, Ly H et al. Quantitation of CXCR4 expression in myocardial infarction using 99mTc-labeled SDF-1alpha. J Nucl Med 2008;49:963–969.

95 Hiesinger W, Frederick JR, Atluri P et al. Spliced stromal cell-derived factor-1alpha analog stimulates endothelial progenitor cell migration and improves cardiac function in a dose-dependent manner after myocardial infarction. J Thorac Cardiovasc Surg 2010;140:1174–1180.

96 Hiesinger W, Perez-Aguilar JM, Atluri P et al. Computational protein design to reengineer stromal cell-derived factor-1alpha generates an effective and translatable angiogenic polypeptide analog. Circulation 2011;124:18–26.

97 Segers VF, Tokunou T, Higgins LJ et al. Local delivery of protease-resistant stromal cell derived factor-1 for stem cell recruitment after myocardial infarction. Circulation 2007;116:1683–1692.

98 Wysoczynski M, Reca R, Ratajczak J et al. Incorporation of CXCR4 into membrane lipid rafts primes homing-related responses of hematopoietic stem/progenitor cells to an SDF-1 gradient. Blood 2005;105:40–48.

99 Ratajczak MZ, Kim CH, Abdel-Latif A et al. A novel perspective on stem cell homing and mobilization: Review on bioactive lipids as potent chemoattractants and cationic peptides as underappreciated modulators of responsiveness to SDF-1 gradients. Leukemia 2012;26:63–72.

100 Basu S, Broxmeyer HE. Transforming growth factor-beta1 modulates responses of CD34+ cord blood cells to stromal cell-derived factor-1/CXCL12. Blood 2005;106:485–493.

101 Bernal A, San Martin N, Fernandez M et al. L-Selectin and SDF-1 enhance the migration of mouse and human cardiac mesoangioblasts. Cell Death Differ 2012;19:345–355.

102 Drury LJ, Ziarek JJ, Gravel S et al. Monomeric and dimeric CXCL12 inhibit metastasis through distinct CXCR4 interactions and signaling pathways. Proc Natl Acad Sci USA 2011;108:17655–17660.

103 Ray P, Lewin SA, Mihalko LA et al. Secreted CXCL12 (SDF-1) forms dimers under physiological conditions. Biochem J 2012;442:433–442.

104 Poznansky MC, Olszak IT, Foxall R et al. Active movement of T cells away from a chemokine. Nat Med 2000;6:543–548.

105 Brooks HL, Jr., Caballero S, Jr., Newell CK et al. Vitreous levels of vascular endothelial growth factor and stromal-derived factor 1 in patients with diabetic retinopathy and cystoid macular edema before and after intraocular injection of triamcinolone. Arch Ophthalmol 2004;122:1801–1807.

106 Kucia M, Reca R, Miekus K et al. Trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms: Pivotal role of the SDF-1-CXCR4 axis. Stem Cells 2005;23:879–894.

107 Ratajczak MZ, Zuba-Surma E, Kucia M et al. The pleiotropic effects of the SDF-1-CXCR4 axis in organogenesis, regeneration and tumorigenesis. Leukemia 2006;20:1915–1924.

108 Oh SB, Tran PB, Gillard SE et al. Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci 2001;21:5027–5035.

109 Knerlich-Lukoschus F, von der Ropp-Brenner B, Lucius R et al. Spatiotemporal CCR1, CCL3(MIP-1alpha), CXCR4, CXCL12(SDF-1alpha) expression patterns in a rat spinal cord injury model of posttraumatic neuropathic pain. J Neurosurg Spine 2011;14:583–597.

110 Zhang H, Trivedi A, Lee JU et al. Matrix metalloproteinase-9 and stromal cell-derived factor-1 act synergistically to support migration of blood-borne monocytes into the injured spinal cord. J Neurosci 2011;31:15894–15903.

111 Sánchez-Martín L, Estecha A, Samaniego R et al. The chemokine CXCL12 regulates monocyte-macrophage differentiation and RUNX3 expression. Blood 2011;117:88–97.

112 Martinez FO, Gordon S, Locati M et al. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: New molecules and patterns of gene expression. J Immunol 2006;177:7303–7311.