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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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.

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,
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<sup>+</sup> adult bone marrow-derived stem cells do not express...
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 surrounding 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 remylinate 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

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**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.
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-1α⁻/⁻ 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 oncogetic 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.
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