Review

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The role of C-X3-C motif chemokine ligand 1/C-X3-C motif chemokine receptor 1 axis in spinal cord injury

Longyu Li[a], Zikuan Leng[a], Songfeng Chen[a], Hongjian Liu[a,*]

Abstract: Spinal cord injury (SCI) is often accompanied by significantly enhanced neuroinflammation. The regulation of neuroinflammation may be a potential direction for SCI repair. Cellular communication and interaction between neurons and microglia can affect the level of neuroinflammation and thereby influence SCI repair and function recovery. Increasing evidence highlights that the C-X3-C motif chemokine ligand 1/C-X3-C motif chemokine receptor 1 (CX3CL1/CX3CR1) axis plays a central role in this process. Here, we review the relevant studies on CX3CL1 and CX3CR1 in the field of SCI and summarize the structural characteristics of *CX3CL1* and *CX3CR1* and their spatiotemporal expression features after SCI. In addition, the bidirectional role of CX3CL1/CX3CR1 axis in neuroinflammation and possible treatment methods focused on CX3CL1/CX3CR1 axis are also discussed. CX3CL1/CX3CR1 axis acts as a dynamic regulator of neuroinflammation and a potential therapeutic target for SCI repair. Further studies are needed to elucidate the spatiotemporal mechanisms of this axis and guide its clinical translation.

Abbreviations: SCI = spinal cord injury, CX3CL1 = C-X3-C motif chemokine ligand 1, CX3CR1 = C-X3-C motif chemokine receptor 1, CNS = central nervous system, ADAM10 = metalloproteinase 10, CatS = cathepsin S, Dpi = days post injury, scRNA-seq = single-cell RNA sequencing, TNF-α = tumor necrosis factor-α, IL-1β = interleukin-1β, IL-6 = interleukin-6, NF-κB = nuclear factor-κB, p38 MAPK = p38 mitogen-activated protein kinase, ATP = adenosine triphosphate, P2X7 = P2X, ligand-gated ion channel, 7, M-CSF = macrophage colony-stimulating factor.

Keywords: CX3CL1, CX3CL1/CX3CR1 axis, CX3CR1, neuroinflammation, spinal cord injury

1. Introduction

Spinal cord injury (SCI) is a severe and disabling condition, frequently resulting from traffic accidents and falls from elevated heights. It commonly leads to partial or complete impairment of sensory and motor functions below the level of the injury.[1] Epidemiological studies indicate that the prevalence of SCI in China is 358 cases per 100,000 individuals, with the total number of affected patients close to 16 million globally.[2–4] Current clinical management for SCI and resulting paraplegia primarily relies on surgical decompression supplemented by corticosteroid pulse therapy and rehabilitation training.[5] However, existing approaches cannot directly repair damaged spinal cord regions or promote nerve regeneration, resulting in limited therapeutic efficacy. Therefore, it is important to identify key mechanisms or therapeutic targets to repair SCI and promote functional recovery.

The significantly enhanced neuroinflammatory response following SCI plays complex and diverse roles across different postinjury stages. Modulating neuroinflammation may represent a crucial therapeutic direction for repairing SCI and promoting functional recovery.[6] Microglia play an important role in immune regulation and inflammatory responses, interacting with neurons to regulate neural repair after SCI.[7,8] Chemokines, as a class of neuromodulatory molecules, can regulate neuroinflammation by influencing the communication between neurons and microglia. Among these, C-X3-C motif chemokine ligand 1 (CX3CL1) and C-X3-C motif chemokine receptor 1 (CX3CR1) are considered core chemokines in this regulation, and CX3CL1/CX3CR1 axis holds promise as a key therapeutic target for SCI repair.[9] Although several studies have highlighted the important role of CX3CL1/CX3CR1 axis in the central nervous system (CNS),[10–12] its pathophysiological changes and potential functions after SCI remain inadequately and unsystematically characterized. This review provides a comprehensive overview of the spatiotemporal dynamics of CX3CL1/CX3CR1

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axis following SCI, elucidates its underlying function and mechanisms in the progression of SCI, and explores potential therapeutic strategies targeting this axis.

1.1. CX3CL1 and CX3CR1

Based on the number and spatial organization of conserved cysteine residues in their N-terminus, chemokines were initially classified into three subfamilies: C-, CC-, and CXC- (C denotes cysteine and X can be any amino acid). In 1997, Bazan et al.[13] first identified the *CX3C*-type chemokine.

CX3CL1, also known as fractalkine, is the sole member of the CX3C-family. Its encoding genes are located on mouse chromosome 8 (8qC5, [q, long arm]), rat chromosome 19 (19p12, [p, short arm]), and human chromosome 16 (16q13).[14–16] CX3CL1 is a unique chemokine existing in both membrane-bound and soluble (sCX3CL1) forms. Its dual existence confers both adhesive and chemotactic properties. As one of two known transmembrane-anchored chemokines, its membrane-bound form comprises a chemokine domain, mucin-like stalk structure, transmembrane domain, and cytoplasmic tails. It can be cleaved into soluble forms at multiple sites by proteases, including a disintegrin and metalloproteinase 10 (ADAM10), ADAM17, and cathepsin S (CatS) at distinct sites to generate the soluble form.[17,18] In the CNS, CX3CL1 is specifically expressed only in mature neurons and signals exclusively through its receptor CX3CR1.[19] CX3CR1 belongs to the chemokine receptor superfamily, possessing 7 transmembrane G-protein-coupled domains (Fig. 1), and its encoding genes are located on mouse chromosome 9 (9qF4), rat chromosome 8 (8q32), and the short arm of human chromosome 3 (3p21.3).[20,21] It should be noted that although CX3CL1 and CX3CR1 have a unique ligand–receptor relationship, CX3CR1 is not exclusively expressed in a single cell type like CX3CL1. Instead, it is expressed in multiple cell types, including monocytes, natural killer cells, T cells, and smooth muscle cells, predominantly in microglia.[22] In other words, the interaction and signaling between CX3CL1 and CX3CR1 are not entirely equivalent to the cellular communication between neurons and microglia.

2. Dynamic changes of CX3CL1/CX3CR1 axis after SCI

2.1. Temporal expression characteristics of CX3CL1/CX3CR1 axis after SCI

Several studies have demonstrated the mRNA and protein expression changes of *CX3CL1* and *CX3CR1* at different time points after SCI (Fig. 2). Both mRNA and protein expression of *CX3CL1* reduce significantly during 1 to 7 days postinjury (dpi), accompanied by a sharp increase in the level of *CX3CR1* mRNA expression.[23] Chen et al.[24] presented the variations of both CX3CL1 and CX3CR1 in detail, proving that their expression levels reach the peak simultaneously at 10 dpi and return to baseline levels at 14 and 28 dpi.

The change in the expression level of CX3CL1 over time confirms that it has the characteristics of both membrane-bound and soluble types. Currently, most studies support that signaling and transmission within CX3CL1/CX3CR1 axis primarily rely on sCX3CL1. It seems that membrane-bound CX3CL1 also appears

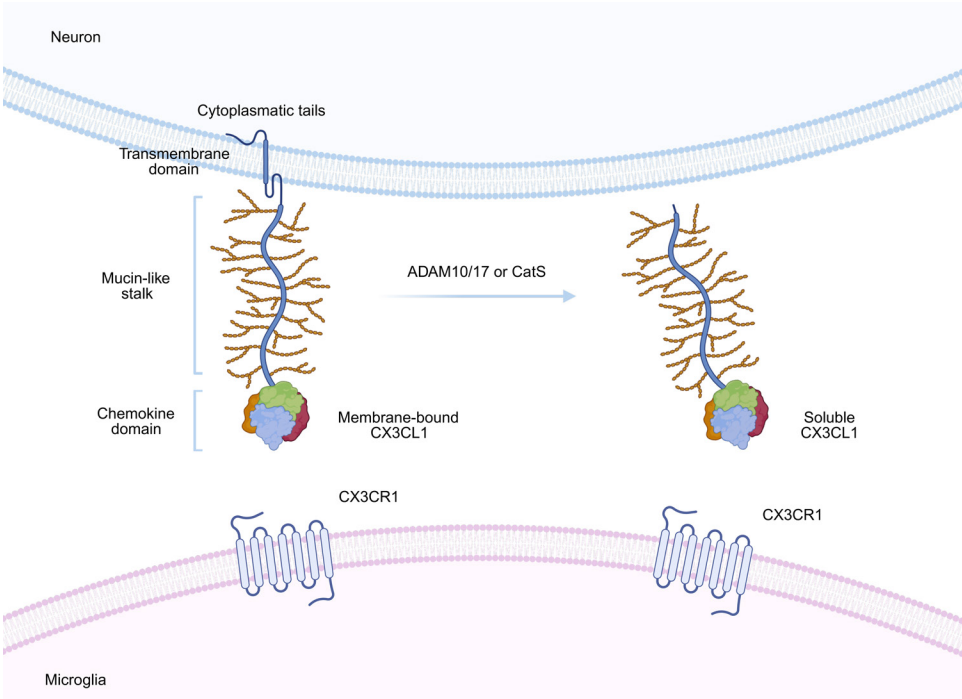


Figure 1. Diagrammatic representation of the structure of CX3CL1 (membrane-bound and soluble forms) and CX3CR1. Created in BioRender.

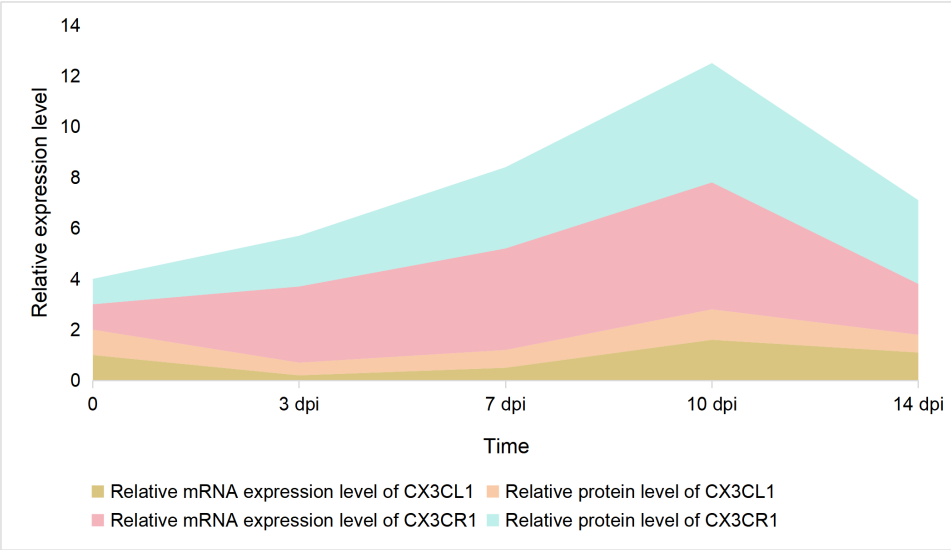


Figure 2. Temporal expression characteristics of CX3CL1 and CX3CR1 after SCI. dpi = days postinjury.

capable of binding CX3CR1, although it may yield different functional outcomes.[9] The decrease of CX3CL1 expression during the acute phase of SCI can be interpreted as the result of a shift between membrane-bound and soluble forms. Because some studies have shown that when the brain or spinal cord is damaged, total expression of *CX3CL1* mRNA remains unchanged, while the protein expression of membrane-bound CX3CL1 is reduced.[25] Although the expression of CX3CL1 subsequently recovers and stabilizes, its spatial distribution patterns may influence the expression and distribution of CX3CR1-positive cells, thereby limiting neural regeneration and functional recovery after SCI. CX3CR1 is primarily expressed on microglia in the CNS, and the dynamic process of its expression is closely linked to the activation of microglia. The result of single-cell RNA sequencing (scRNA-seq) revealed that the acute phase (1–3 dpi) after SCI represents the first peak of microglial activation, which temporally corresponds to a significant increase in CX3CR1 expression.[26] At this time, the significant reduction in CX3CL1 weakens its inhibitory effect on microglial activation. Consistent with these findings, another study based on scRNA-seq similarly demonstrated that during the acute phase after SCI, a pronounced elevation of *CX3CR1* expression—characterized by an increased abundance of *CX3CR1*-positive microglia subsets—is accompanied by a robust enhancement of the neuroinflammatory response, highlighting the strong association between CX3CL1/CX3CR1 axis and neuroinflammation.[27]

2.2. Spatial expression characteristics of CX3CL1/CX3CR1 axis and microglia/macrophages after SCI

Wang et al.[28] reported that there is a significant reduction of resident microglia with large infiltration of peripheral macrophages at 3 dpi, according to the result of scRNA-seq, which focuses on immune cells. Because both macrophages and microglia are capable of expressing CX3CR1, their dynamic changes can influence the spatial expression of CX3CL1/CX3CR1 axis and the progression of SCI. Ye et al.[29] elaborated on the spatial distribution characteristics of CX3CL1 and CX3CR1, and their results showed that the expression of CX3CL1 is significantly reduced at the lesion center. Instead, the majority of CX3CL1 is observed at the lesion periphery. The expression of CX3CR1 can be observed both in the lesion center and periphery. Moreover, to distinguish macrophages and microglia and identify the interaction between neurons and microglia, immunofluorescence staining with Fascin-1 (marking microglia) and Mac-2 (marking macrophages) revealed that microglia predominantly aggregate at the lesion periphery and fail to migrate toward the center of the lesion after SCI. CX3CR1-positive cells in the lesion center are primarily macrophages.

The spatial relationship between macrophages and microglia, along with the distribution pattern of CX3CL1/CX3CR1 axis, reveals an important challenge in neural repair and regeneration—namely, that the inability of CX3CL1 to penetrate the injury core leads to the accumulation of CX3CR1-positive microglia around the lesion area, thereby restricting their centripetal chemotaxis and their replacement of macrophages within the injury center.[30] All these temporal and spatial expression changes reflect the evolving role of CX3CL1/CX3CR1 axis throughout the acute and chronic phases of SCI, implicating this chemokine axis as both a regulator and potential biomarker of postinjury neuroimmune responses.

3. Function and mechanism of CX3CL1/CX3CR1 axis in SCI

3.1. Bidirectional regulation in neuroinflammation

One of the features of SCI is a robust secondary inflammatory response mediated by microglia and infiltrating immune cells. Neuroinflammation is central to secondary tissue damage and serves as a double-edged sword, as it contributes to neuronal death, demyelination,

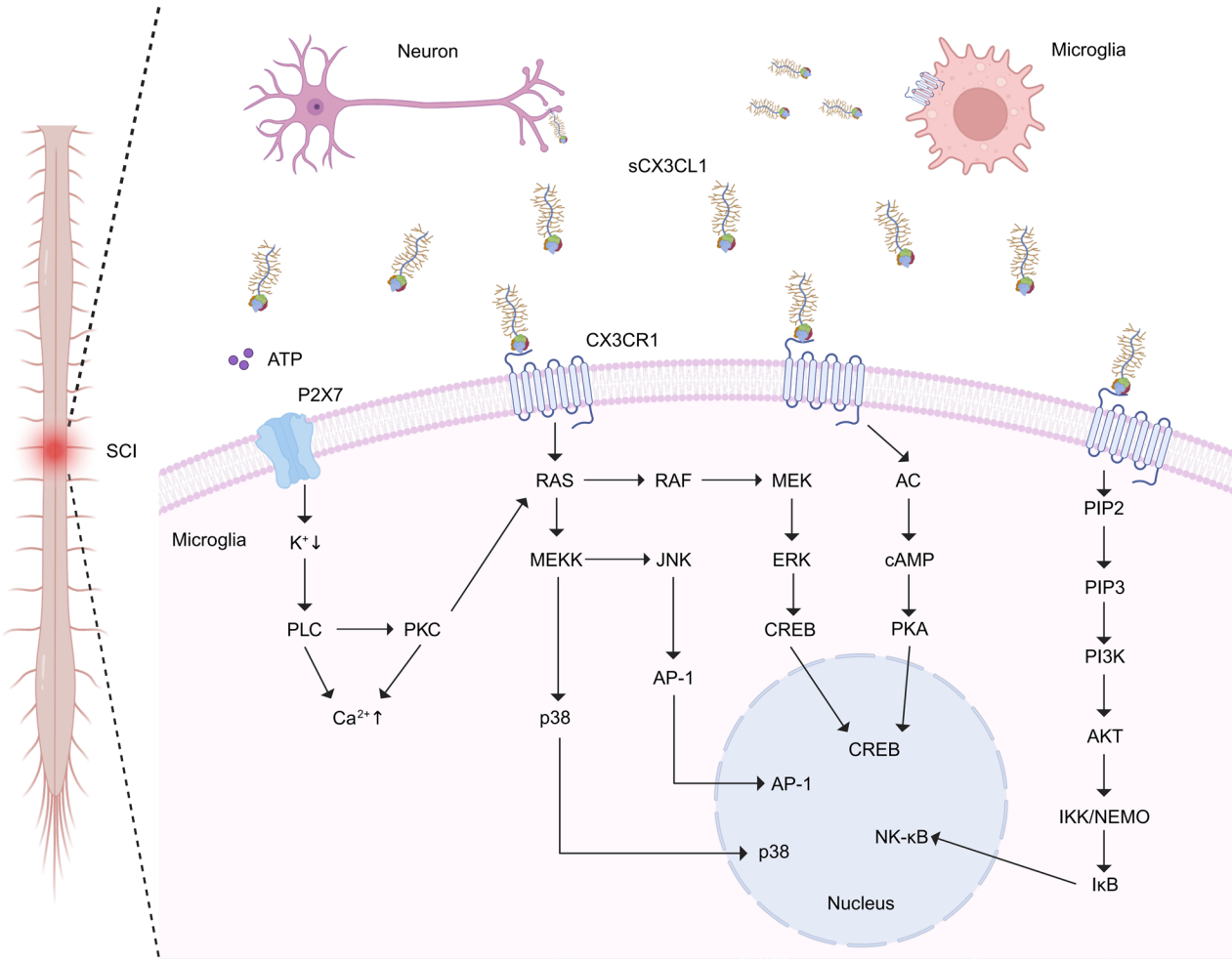


Figure 3. Signaling pathways related to CX3CL1/CX3CR1 axis after SCI. Created in BioRender. AC = adenylyl cyclase, AKT = protein kinase B, AP-1 = activator protein 1, ATP = adenosine triphosphate, cAMP = cyclic adenosine monophosphate, CREB = cAMP response element-binding protein, ERK = extracellular signal-regulated kinase, IκB = inhibitor of κB, IKK/NEMO = IκB kinase/NF-κB essential modulator, JNK = c-Jun N-terminal kinase, MEK = mitogen-activated protein kinase kinase, MEKK = mitogen-activated protein kinase kinase kinase, NK-κB = nuclear factor-κB, PI3K = phosphoinositide 3-kinase, PIP2 = phosphatidylinositol 4,5-bisphosphate, PIP3 = phosphatidylinositol 3,4,5-trisphosphate, PLC = phospholipase C, PKA = protein kinase A, PKC = protein kinase C, RAF = rapidly accelerated fibrosarcoma kinase, RAS = rat sarcoma small GTPase family protein, SCI = spinal cord injury.

and glial scar formation, but also plays a crucial role in debris clearance and repair initiation.[31,32] CX3CL1/CX3CR1 axis significantly influences the communication and interaction between neurons and microglia in the CNS, which occupies a central role in regulating neuroinflammation and the activity of microglia (Fig. 3).

At present, research of CX3CL1/CX3CR1 axis on neuroinflammation in CNS mainly focuses on brain diseases, including stroke, Alzheimer disease, Parkinson syndrome, and so on. However, the regulatory effect of this axis on neuroinflammatory response varies across different diseases. For example, CX3CL1 deficiency in stroke may reduce cerebral infarct size.[9] In contrast, compared with normal people, patients with Alzheimer disease have a lower level of CX3CL1 in the cerebrospinal fluid and cerebral cortex.[33] Furthermore, compared with the elderly without cognitive impairment, patients with mild cognitive impairment had higher concentrations of CX3CL1 in the blood and cerebrospinal fluid.[34] Thus, the regulation effect of CX3CL1/CX3CR1 axis on neuroinflammation is highly complex and diverse, exhibiting both disease specificity and strong sensitivity to spatiotemporal changes.

Cardona et al.[35] and Li et al.[36] demonstrated that under physiological conditions, the expression level of CX3CL1 limits excessive activation of microglia and maintains a stable expression level of CX3CR1 in mice and rats, respectively. However, SCI disrupts this balance—damaged neurons release increased amounts of sCX3CL1, and CX3CR1 expression is markedly upregulated on activated microglia and infiltrating macrophages.[37]

Accumulating evidence indicates that the CX3CL1/CX3CR1 axis exerts context-dependent and bidirectional effects on neuroinflammation following SCI. In the acute phase, enhanced CX3CL1/CX3CR1 signaling may amplify microglial activation and promote the

production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) via the nuclear factor-κB (NF-κB) and p38 mitogen-activated protein kinase (p38 MAPK) pathways, thereby aggravating secondary tissue injury. Conversely, during the subacute and chronic stages, the same signaling pathways can attenuate excessive inflammation, promoting neuronal survival and functional recovery after SCI.[19] For example, Lv et al.[38] found that CX3CL1 is supposed to regulate ferroptosis and oxidative stress-related pathways in microglia *in vitro* based on transcriptomic analysis, preliminarily confirming the neuroprotective effect of CX3CL1 in SCI. Subsequent studies in mice further demonstrated that CX3CL1/CX3CR1 axis can modulate inflammation mediated by microglia via the NF-κB pathway, thereby enhancing neuronal survival and functional recovery after SCI. Donnelly et al.[23] observed that blocking *CX3CR1* signaling inhibits macrophage recruitment and reduces their capacity to synthesize and release inflammatory cytokines and oxidative metabolites, resulting in a neuroprotective effect in SCI mice. Therefore, CX3CL1/CX3CR1 functions as a dynamic regulator of neuroinflammation in SCI, capable of both exacerbating and resolving inflammatory damage depending on the timing and cellular context of activation. Further extensive research is required to elucidate its specific mechanisms.

3.2. Neuropathic pain

Neuropathic pain is one of the most frequent and debilitating complications following SCI, and its pathogenesis is tightly associated with chronic neuroinflammation and microglial overactivation in the spinal dorsal horn.[39,40] Among the numerous chemokine systems involved, the CX3CL1/CX3CR1 axis plays a pivotal role in linking neuronal injury to microglial activation and the initiation of central sensitization.

Kawano et al.[41] found that the damaged neurons release large amounts of adenosine triphosphate, which is able to activate purinergic receptor P2X, ligand-gated ion channel, 7 (P2X7) receptors (ligand-gated potassium channels) on the surface of microglia, causing the reduction of intracellular K^+ concentration, subsequently activating phospholipase C to elevate intracellular Ca^{2+} concentration. This series of reactions promotes the phosphorylation and activation of p38 MAPK.[42] Simultaneously, CatS converts membrane-bound CX3CL1 to sCX3CL1. After the combination of s*CX3CL1* and *CX3CR1*, microglia are activated, and several kinds of proinflammatory factors, such as TNF-α and IL-1β, are released, forming a sustained inflammatory cascade.[43] The persistent neuroinflammation further induces neuropathic pain.[44,45] The activation of CX3CL1 caused by p38 MAPK and CatS not only amplifies neuroinflammation but also induces CX3CL1-mediated mechanical and thermal hyperalgesia.[42,43] This manifests as CX3CL1/CX3CR1 axis, enhancing synaptic transmission in pain-related pathways, ultimately transforming persistent neuropathic pain into chronic and intractable pain.

4. Strategies for SCI repair targeting CX3CL1/CX3CR1 axis

4.1. Co-supplementation of CX3CL1 and macrophage colony-stimulating factor (M-CSF) in situ

The disruption of the blood–spinal cord barrier after SCI leads to preferential macrophage infiltration into the center of the lesion. The predominant occupation of macrophages inhibits the migration of CX3CR1-positive microglia toward the center of the injury area, which aggravates neuroinflammation and hinders neural repair.[29,46] Promoting the centripetal migration of microglia and prolonging their residence time in the injury area enables them to replace macrophages and phagocytose and clear the fragments of neuron and myelin sheath, thereby mitigating secondary neuronal injury and promoting neural repair.[47]

Studies confirmed that *in situ* injection of CX3CL1 in the injured area of the spinal cord can significantly promote the centripetal migration of microglia. However, the microglia that migrate into the lesion under this condition rapidly undergo apoptosis, resulting in a significant decrease in the concentration of microglia at the center of the lesion at 28 dpi, preventing the recovery of spinal cord function. Further studies revealed that co-supplementing CX3CL1 with macrophage colony-stimulating factor (M-CSF) can not only enhance centripetal migration of microglia but also significantly prolong the survival time of these cells, achieving the replacement of macrophages successfully, promoting injured area recovery and axonal regeneration finally (Fig. 4).[29] The function of M-CSF in this process likely involves inhibiting microglial apoptosis and promoting its proliferation.[48] Therefore, it can be seen that SCI repair requires not only to increase CX3CL1 levels at the injured area to recruit microglia centripetally but also to maintain the concentrations of CX3CR1 and microglia to facilitate function recovery. It is co-supplementation of CX3CL1 and M-CSF *in situ* that represents a potential strategy for SCI repair.

4.2. AZD8797: a kind of inhibitor of CX3CR1

AZD8797 is a kind of selective and high-affinity inhibitor of CX3CR1,[49] which can noncompetitively replace and block the binding of CX3CL1 and CX3CR1 through an allosteric binding mechanism. AZD8797 can increase the dissociation rate of CX3CL1, reduce the affinity of CX3CR1 for CX3CL1, and ultimately achieve the effect of replacing CX3CL1 and binding to *CX3CR1*.[50] AZD8797 has the ability to modulate CX3CR1-associated G-protein signaling and β-blocking protein recruitment. However, AZD8797 does not compete directly with CX3CL1 for the orthosteric site, but instead reduces CX3CL1 signaling efficacy by altering receptor conformation and downstream signal coupling,

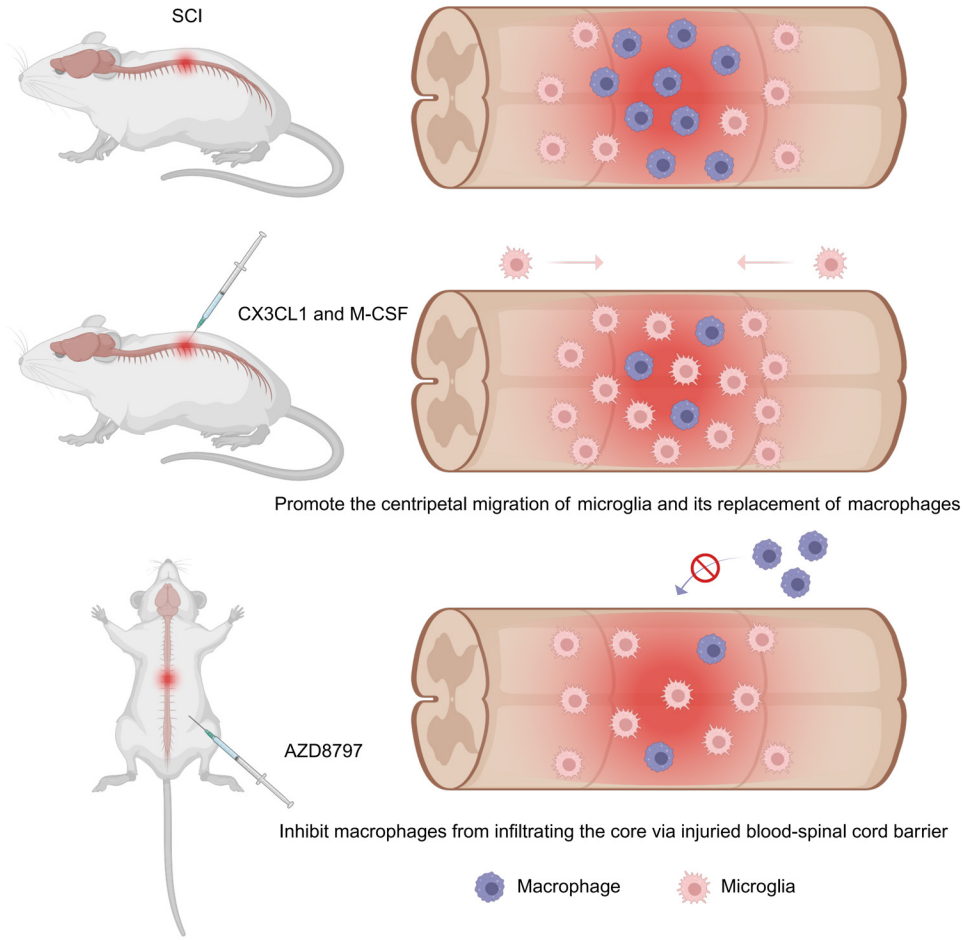


Figure 4. Comparison of 2 kinds of therapeutic strategies for SCI repair targeting CX3CL1/CX3CR1 axis. Created in BioRender. SCI = spinal cord injury.

potentially reducing proinflammatory microglial activation and leukocyte recruitment driven by CX3CL1/CX3CR1 axis. Furthermore, β-blocking protein recruitment experiments confirm that AZD8797 positively regulates CX3CL1 and enhances its expression level through a positive feedback loop.

Although AZD8797 appears peripherally restricted in distribution after systemic dosing, its immunomodulatory effects—likely via inhibition of CX3CR1-expressing monocytes and macrophages from infiltrating the CNS—translated into downstream reductions in central inflammation and tissue damage (Fig. 4). The study in a rat SCI model showed that AZD8797 administration in the acute phase after injury suppressed excessive inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6), inhibited apoptosis and necrosis in injured spinal cord, and improved early locomotor recovery, effects comparable in magnitude to methylprednisolone.[24] These findings further support the ability of AZD8797 to act on CX3CL1/CX3CR1 axis for SCI repair and promote function recovery, demonstrating its broad prospects for clinical application in SCI repair.

Despite promising preclinical outcomes, several limitations constrain the translational potential of AZD8797 for SCI. From pharmacokinetics, systemic administration resulted in limited CNS penetration in rodent models, suggesting its effects may primarily accrue via peripheral immune modulation rather than direct central action. Besides, although AZD8797 exhibits high affinity to both human and rat CX3CR1, species differences implied that dose and efficacy may not scale linearly from rodents to humans. To date, no clinical trials have assessed AZD8797 in SCI or other CNS conditions, and human safety profiles remain to be established. In addition, as a noncompetitive allosteric modulator with biased signaling, the net biological effects can be context-dependent.

5. Outlook

Due to the complex morphology of the CNS and the unique immune microenvironment at the injured area of spinal cord, current conclusions on CX3CL1/CX3CR1 axis remain inconsistent and contradictory in some cases. This axis appears to exert bidirectional regulation on microglia and neuroinflammation. This phenomenon may be closely related to the number and distribution of microglia in the spinal cord, the extent of blood–brain barrier disruption, and spatiotemporal changes after SCI.[51] Encouraging outcomes have emerged from several studies

targeting CX3CL1/CX3CR1 axis. Function recovery is observed in both mice and rats, suggesting that CX3CL1/CX3CR1-targeted therapies hold promise for SCI repair and function recovery. However, translation to clinical application remains challenging. Given the dynamic and phase-dependent nature of CX3CL1/CX3CR1 signaling, future therapies will require precise temporal control—inhibiting early deleterious inflammation while promoting later repair and remyelination.

CX3CL1/CX3CR1 axis represents both a therapeutic target and a pathophysiological indicator of SCI. Future work should emphasize context-dependent modulation and integrated molecular mapping to fully harness its potential for promoting neural repair and functional recovery. Advanced methodologies such as spatial transcriptomics and *in situ* proteomics will be instrumental in delineating the cell-type-specific and regional dynamics of CX3CL1 and CX3CR1 expression throughout the SCI process. Integrating these tools with multiomics analyses and imaging-based immune profiling will help unravel how CX3CL1/CX3CR1 axis interfaces with other pathways. Additionally, quantification of sCX3CL1 in cerebrospinal fluid or plasma holds promise as a minimally invasive biomarker for assessing injury severity, prognosis, or response to CX3CR1-targeted interventions.

6. Conclusions

Modulating CX3CL1/CX3CR1 axis provides a promising avenue to rebalance neuroinflammation and enhance neural repair following SCI. This axis orchestrates the bidirectional communication between neurons and microglia, exerting distinct effects across injury phases—initially amplifying inflammatory signaling, then promoting resolution and regeneration. Therapeutic interventions targeting this pathway have yielded encouraging results. Nevertheless, the translational application of these strategies faces challenges. Future research should employ spatial-temporal omics profiling to map cell-specific expression patterns, integrate multiomics and imaging-based immune analyses, and identify sCX3CL1 as a potential biomarker for disease monitoring and therapeutic response. Overall, precise, phase-specific modulation of the CX3CL1/CX3CR1 axis—balancing inflammation suppression with tissue regeneration—may pave the way for next-generation, mechanism-driven treatments to restore function after SCI.

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Ethical statement

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions

LL, ZL, and SC—drafted the manuscript.
HL—edited the final manuscript.
LL, ZL, SC, and HL—reviewed and approved the final submitted manuscript.

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