Brain, Behavior, & Immunity - Health 43 (2025) 100932

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

The role of CXCL12/CXCR4/CXCR7 axis in cognitive impairment associated with neurodegenerative diseases

Rojin Sarallah [a], Shima Jahani [b], Alireza Soltani Khaboushan [c], Amir Kian Moaveni [c], Maryam Amiri [c], Masoumeh Majidi Zolbin [c,*]

[a] Islamic Azad University, Tehran, Iran
[b] MS Research Center Neuroscience Institute, Tehran University of Medical Science, Iran
[c] Pediatric and Urology and Regenerative Medicine Research Center, Gene, Cell and Tissue Research Institute, Children Medical Hospital, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
CXCL12
CXCR4
CXCR7
Cognitive impairment
Neurodegenerative diseases

ABSTRACT

Neurodegenerative diseases, including Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS), are characterized by progressive neuronal loss and cognitive impairment (CI). The: Cysteine-X-cysteine chemokine ligand 12(CXCL12)/CXC chemokine receptor type 4 (CXCR4)/CXC chemokine receptor type 7 (CXCR7) axis has emerged as a critical molecular pathway in the development of CI in these disorders. This review explores the role of this axis in the pathogenesis of CI across these neurodegenerative diseases, synthesizing current evidence and its implications for targeted therapies. In AD, dysregulation of this axis contributes to amyloid-β accumulation and tau hyperphosphorylation, leading to synaptic dysfunction and cognitive decline. PD studies reveal that CXCL12/CXCR4 signaling influences dopaminergic neuron survival and microglial activation, affecting cognitive function. In MS, the axis modulates neuroinflammation and demyelination processes, impacting cognitive performance. ALS research indicates that the CXCL12/CXCR4/CXCR7 pathway is involved in motor neuron degeneration and associated cognitive deficits. Across these diseases, the axis influences neuroinflammation, synaptic plasticity, and neuronal survival through various signaling cascades, including PI3K/AKT, MAPK, and JAK/STAT pathways. Emerging evidence suggests that modulating this axis could provide neuroprotective effects and potentially alleviate cognitive symptoms. This review highlights the potential of the CXCL12/CXCR4/CXCR7 axis as a therapeutic target for addressing CI in neurodegenerative diseases. It also underscores the need for further research to fully elucidate its role and develop effective interventions, potentially leading to improved clinical management strategies for these devastating disorders.

1. Introduction

Neurodegenerative diseases are a group of disorders characterized by the progressive loss of neurons in the central nervous system (CNS), leading to cognitive impairment (CI) and other neurological symptoms (McDonald, 2017). AD, PD, ALS, and MSare among the most common neurodegenerative diseases (Gonzales et al., 2022). CI is a frequent complication of these diseases, affecting millions of individuals worldwide. It is characterized by deficits in memory, attention, executive function, visuospatial functioning, abstract reasoning, and information processing speed, which can significantly impact an individual's quality of life (Giannakopoulos et al., 2009; Lindeboom and Weinstein, 2004). The global elderly population is increasing, leading to a rise in age-related neurological diseases causing cognitive decline(Perez et al., 2012; Sarailoo et al., 2022). The etiology of neurodegenerative diseases is multifaceted and involves genetic factors, environmental influences, and inflammatory processes. One of the molecular pathways implicated in the pathophysiology of cognitive impairment in neurodegenerative diseases is the CXCL12/CXCR4/CXCR7 axis. (Shi et al., 2020; Yan et al., 2022). This axis contains chemokine CXCL12 and its receptors which are essential for chemoattractant and functioning of immune system. It is clear that any dysregulation of chemokine production frequently leads

* Corresponding author. Pediatric Urology and Urology and Regenerative Medicine Research Center, Gene, Cell and Tissue Research Institute, Children Medical Hospital, Tehran University of Medical Sciences, Tehran, Iran.
E-mail addresses: mmajidizolbin@sina.tums.ac.ir, Masoumeh.majidizolbin@gmail.com (M. Majidi Zolbin).

https://doi.org/10.1016/j.bbih.2024.100932
Received 11 August 2024; Received in revised form 3 December 2024; Accepted 21 December 2024
Available online 24 December 2024

to disease(García-Cuesta et al., 2019)**(10).** Under inflammatory conditions, CXCL12/CXCR4/CXCR7 interaction results in several pivotal physiological and pathological processes, including neurogenesis, neuromodulation, neuroinflammation, and neuroprotection (Bonavia et al., 2003; Engelhardt and Ransohoff, 2012; Xiang et al., 2002). CXCL12/CXCR4/CXCR7 signaling transduction directs the chemotaxis of microglia and other CNS-resident immune cells into injured sites, leading to neuronal loss in areas responsible for cognition and cognitive impairment. (Fig. 1)

Additionally, activation of these signaling pathways can promote the expression of transcription factors related to neurodegenerative genes, such as NF-κB and AP-1, which play important roles in Alzheimer's and Parkinson's diseases(Yan et al., 2022; Long et al., 2021; Guyon, 2014). Dysregulation of this axis has been implicated in many neurodegenerative diseases, including AD, PD, MS, and ALS (Shimoji et al., 2009)

This paper delves into the CXCL12/CXCR4/CXCR7 axis and its role in the pathophysiology of cognitive impairment in neurodegenerative diseases. The report will also investigate the genetic variations associated with cognitive impairment in this axis and their functional consequences. Understanding the genetic basis of cognitive impairment based on the CXCL12/CXCR4/CXCR7 axis is essential, as it will aid in developing targeted therapeutic strategies(Zilkha-Falb et al., 2016; Zella et al., 2019).

2. CXCL12/CXCR4/CXCR7 axis: molecular mechanisms and signaling pathways

2.1. CXCL12 (SDF-1): structure and function

CXCL12, also known as SDF-1, is a chemokine that plays crucial roles in regulating neovascularization, tissue homeostasis, stem cell growth, cell migration, and various developmental processes such as neurogenesis, B cell development, neurotransmission, progenitor cell differentiation, and apoptosis(Zlotnik and Yoshie, 2000; Lapidot et al., 2005). CXCL12 is primarily expressed in regions responsible for cognitive regulation in the CNS. Besides, several studies on animal models have proven the alteration in CXCL12/CXCR7/CXCR4 proportions in the neuro-inflammation conditions, triggers the activation of glial cells and leads early gene expression and cell proliferation in learning areas. Ultimately affecting the mice's learning abilities(Yan et al., 2022; Trousse et al., 2019).

This cytokine can be secreted from various sites originating from different embryonic layers, such as astrocytes arising from ectoderm and $CD4^{+}$ T-cells arising from mesoderm (Luo et al., 2016a; de Bock and Cools, 2015).

Previous studies have shown that CXCL12 and its receptors activate several signaling pathways in neurodegeneration processes, including the mitogen-activated protein kinase (MAPK) pathway, also known as the stress-related protein kinase pathway, which can influence neural loss. Other pathways include p38 MAPK (regulating synaptic plasticity), PKC-β (regulating intracellular Ca2+ release for neurotransmission), direct effects on GIRK and Ca2+ channels, and the PI3K/AKT/ERK1,2 pathway (modulating apoptosis, normal synaptic plasticity, and neuroprotection). These pathways, directly and indirectly, stimulate transcription factors and other mediators essential for neuronal loss or preservation(Matsuda et al., 2019; Sugiyama et al., 2019).

2.2. CXCR4: receptor characteristics and signaling

CXCR4 is a transmembrane G-protein coupled receptor that functions as a receptor for CXCL12 and plays a significant role in the development of the nervous system. It participates in several biological events, including organogenesis, hematopoiesis, and immune response. In neuroinflammation, the dysregulation of CXCR4 has been implicated in diseases such as HIV-associated disease and cancer. The release of CXCR4 is associated with the trafficking of monocytes into injured sites.

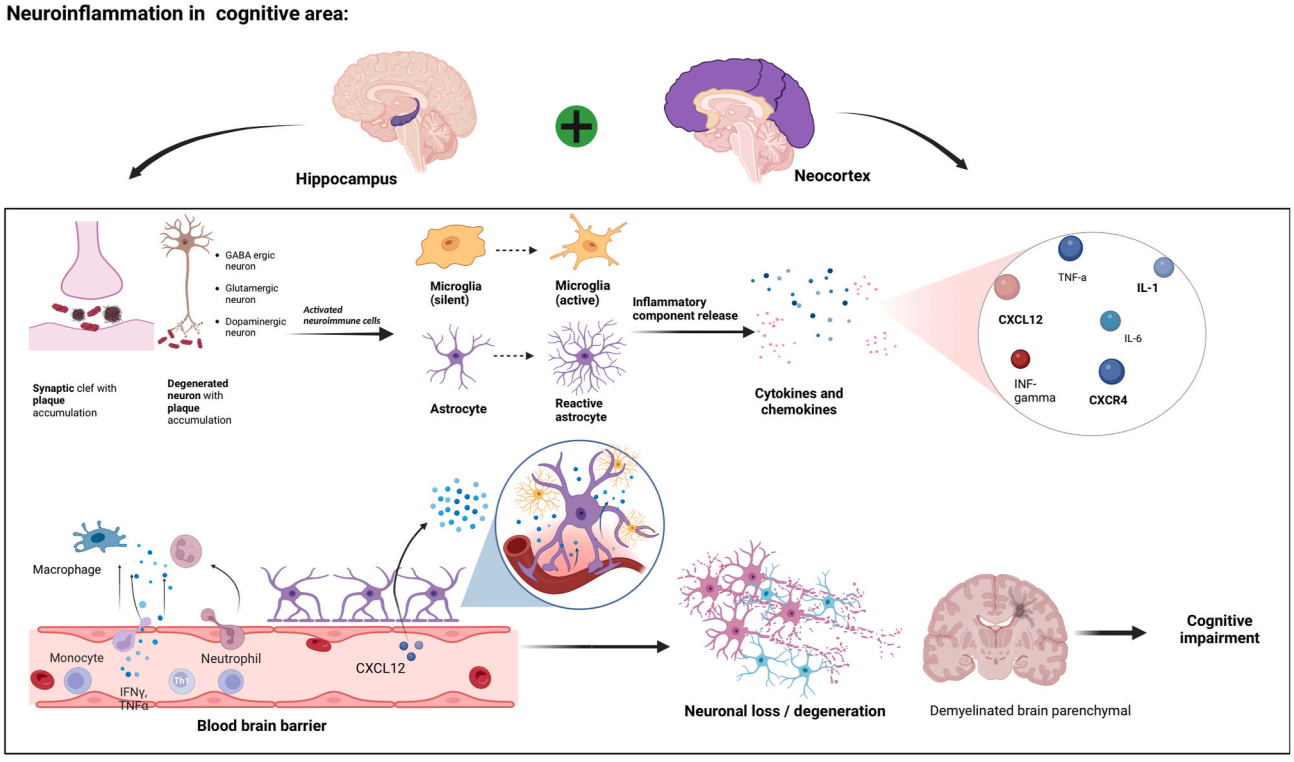

Fig. 1. Neuroinflammation and cognitive impairment
Under inflammatory processes in the brain, plaques accumulate in the synaptic cleft. CNS-resident immune cells, including neuroglia and astrocytes, become activated through signaling pathways and release several cytokines and chemokines, such as CXCL12. The interaction of these chemokines triggers neuronal loss and degeneration in areas related to learning.

Embryologically, CXCR4 is derived from the mesoderm and endoderm layers(Terheyden-Keighley et al., 2022). In the CNS, CXCR4 is expressed in glial cells, particularly astrocytes, and some neurons called neuronal progenitor cells (NPC). These cells can release CXCR4 in response to inflammation. Regions in the CNS that can produce CXCR4 include the cerebral cortex, globus pallidus, lateral hypothalamus, substantia nigra, and cerebellum(Reaux-Le Goazigo et al., 2012; Mithal et al., 2012). The interaction between CXCL12 and CXCR4 follows two mechanisms: CXCR4-mediated G-protein signaling pathway and independent-G-protein cascade, which recruit β-arrestin(Guyon, 2014; Chu et al., 2017; Dziembowska et al., 2005). In neurodegenerative diseases (NDDs), CXCR4 is upregulated to adjust to nerve injury and plaque accumulation. The interaction of CXCR4 with its ligand modulates T-cell and B-cell maturation, thereby enhancing the inflammatory process. Previous studies have shown that CXCR4 signaling recruits microglia to remove degenerated neurons and related plaques or attack neuronal sheets(McQuade et al., 2020; Williams et al., 2014; Yamasaki et al., 2014).

CXCR4 stimulation by its ligand has been demonstrated to regulate the synaptic release of glutamate, γ-aminobutyric acid (GABA), and dopamine in various brain structures, including the hippocampus (Zheng et al., 1999), frontoparietal cortex, cerebellum (Limatola et al., 2000), substantia nigra (Banisadr et al., 2005), and dorsal raphe nucleus (Guyon et al., 2005, 2013). The intracellular signaling pathways involved in neurotransmitter release in the cognition area are known as ERK and PI3-K pathways(Guyon, 2014). The PI3K/Akt pathway and Ca2+ mobilization promote GABA and glutamate release. Additionally, CXCR4 activation in astrocytes via TNF-α signaling leads to the release of glutamate(Heinisch and Kirby, 2010; Qu et al., 2008).

2.3. CXCR7: atypical chemokine receptor and its role

CXCR7 is an atypical chemokine receptor 3 (ACKR3), also known as a decay receptor due to its properties in ligand degradation. Its ligands are CXCL12 and CXCL11 (I-TAC). Monocytes, natural killer cells (NK), a limited population of $CD4^+$ T cells, astrocytes, microglia cells, cerebral blood vessels, oligodendrocyte progenitors, neurons, and Schwann cells can express CXCR7 on their membranes(Shimizu et al., 2011; Sánchez-Alcañiz et al., 2011; Banisadr et al., 2016). Disease-associated microglia (DAMs) have a significant role in neurodegeneration and neuronal loss by releasing chemokines, phagocytosis, and inducing disease-related gene expression(Muzio et al., 2021; Lauro and Limatola, 2020). DAMs have lysosomal and lipid metabolism properties, which help in the removal of foreign particles with their phagolysosome. This leads to the hypothesis that CXCR7 production originates from microglial cells(Muzio et al., 2021; Lauro and Limatola, 2020; Subhramanyam et al., 2019).

In the adult brain, CXCR7 expression is limited only to abnormal conditions(Sánchez-Alcañiz et al., 2011). The trigger for its expression can be any injury that disrupts homeostasis in the brain, such as hypoxia or aberrant plaque accumulation. Binding of CXCR7 to CXCL12 can promote ligand endocytosis, disrupt the lysosome, and recruit apoptotic signaling cascades. By this means, it can regulate the CXCL12 gradient concentration(Sánchez-Martín et al., 2013). Furthermore, it can regulate CXCR4-mediated G protein signaling events by heterodimerization (Levoye et al., 2009; Santagata et al., 2021).

2.4. Interplay of CXCL12/CXCR4/CXCR7 signaling in the CNS

The interplay between CXCL12, CXCR4, and CXCR7 in the CNS is complex and multifaceted. CXCR7 is responsible for sequestering CXCL12 and regulating local chemokine availability to ensure responsiveness of the CXCL12/CXCR4 pathway in interneurons. CXCR7 controls neuronal migration by regulating chemokine signaling and is a β-arrestin-biased receptor that potentiates cell migration and recruits β-arrestin exclusively through MAPK and GRK2(García-Cuesta et al., 2019; Sánchez-Martín et al., 2013). CXCR7 signaling is independent of the G-protein coupling pathway and signals through β-arrestin recruitment. CXCL12 can activate several signaling pathways through CXCR7, including the PI3K/Akt, MAPK, and JAK/STAT3 pathways. CXCR7 can also induce intracellular pathways, such as Akt, MAPK, and JAK/STAT3, through β-arrestin or in heterodimers with CXCR4(Zabel et al., 2009). CXCR7-mediated signaling can activate ERK1/2, Akt, and p38 in cortical astrocytes and Schwann cells(Si et al., 2022).

The association of CXCR4 and CXCR7 causes impaired CXCR4-promoted G protein subunit Gi activation and signaling and promotes activation of alternative downstream β-arrestin-dependent signal transduction pathways(Trousse et al., 2019; Huynh et al., 2020). All the signaling transduction regarding CXCL12/CXCR7 activates microglial cells for phagocytosis of external particles. Since CXCR7 binds to CXCL12, it internalizes CXCL12 simultaneously, promoting lysosomes for degradation. Following recent research, CXCR7 adjusts CXCL12 concentration and solitary prevents chemotaxis. As a result, at a low concentration of CXCL12 intracellularly, chemotaxis decreases(Levoye et al., 2009). In the absence of CXCR7, chemotaxis mediated by CXCR4/CXCL12 is maintained, even though migration may occur erroneously to improper sites due to an unbalanced CXCL12 gradient (Dziembowska et al., 2005; Levoye et al., 2009; Zabel et al., 2009; Carbajal et al., 2011).

Abnormal expression of the CXCL12-CXCR4-CXCR7 axis can lead to unfavorable inflammatory results, including cognitive impairment in neurodegenerative diseases, like Alzheimer's (AD). Modulating the axis can alleviate the severity of neurodegenerative disease outcomes(Chu et al., 2017; Cheng et al., 2017). (Fig. 2).

3. CXCL12/CXCR4/CXCR7 axis in neurodegenerative diseases and cognitive impairment

3.1. Alzheimer's disease (AD)

3.1.1. Pathophysiology of AD and cognitive impairment

AD is an age-related, chronic, progressive disease and the most common example of dementia with cognitive impairment features. The gradual disease progression impairs executive daily routines(Braak et al., 1999). The pathophysiology of AD is characterized by excessive and abnormal amyloid β (Aβ) peptide production from Amyloid Precursor Protein (APP) and aggregation as plaques in the synaptic cleft, promoting primary neurodegeneration in AD(Kelley and Petersen, 2007; Tiwari et al., 2019). As the disease progresses, Aβ oligomerization and over-phosphorylation of cellular stabilizer or tau protein via kinase activity make senile plaques and promote alteration of signaling transduction, which consequently leads to local inflammatory response and subsequent neuronal death in synapses and involved neurons (Tiwari et al., 2019; Nelson et al., 2012). Some kinase activities involved in forming neural fibrillary tangles (hyperphosphorylated tau protein) are known as glycogen synthase kinase 3 (GSK3), extracellular Aβ-activated cyclin-dependent kinase 5 (Cdk5), protein kinase C (PKC), and protein kinase A (PKA) (Gao et al., 2018). Initially, the accumulation of Aβ occurs in temporal and basal neocortex regions. As the disease progresses, it spreads to the hippocampus and cerebral cortex, leading to cognitive impairment throughout the disease progression(Chen and Yan, 2010; Wilson et al., 2012).

3.1.2. CXCL12/CXCR4/CXCR7 axis in AD progression

Following senile plaque accumulation in neurons and synaptic space, chemokines derived from secondary immune responses are released from neuroglia, microglia, and other neuronal cells(Rangaraju et al., 2018). Notably, microglia are activated earlier than astrocytes (Rothhammer et al., 2018). Chemokines (CXCL12, CXCR4, CXCR7) trafficking with activating signaling pathways (JAK/STAT, NF-κB) results in neuronal loss and synaptic dysregulation in cognitive sites, which leads to cognitive impairment(Bonavia et al., 2003; Deczkowska

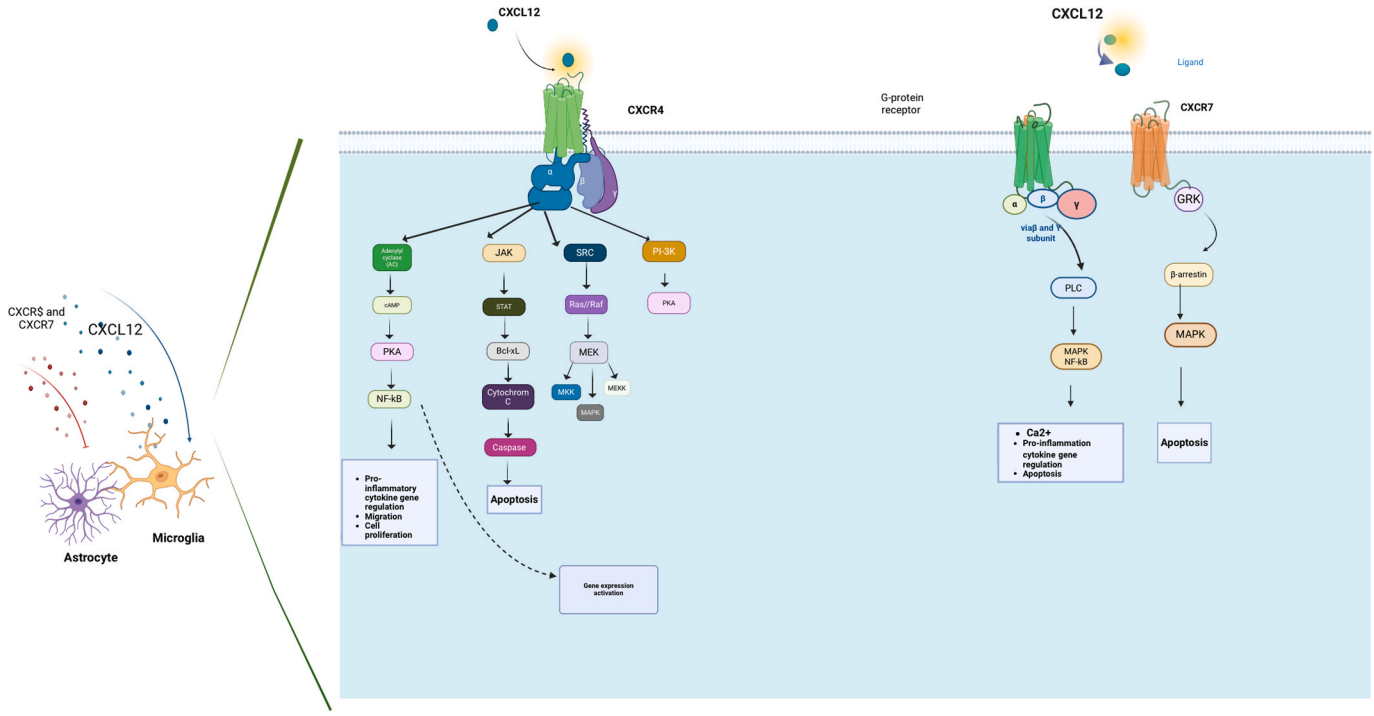

Fig. 2. CXCL12/CXCR4/CXCR7 signaling cascades and their cellular effects
CXCL12 functions by binding to its receptors, CXCR4 and CXCR7. The activation of CXCR4 triggers various signaling pathways including; PI3K/Akt, MAPK, and JAK/STAT3 pathways, whereas CXCR7-mediated signaling can operates independently of the G-protein coupling pathway and instead relies on the recruitment of β-arrestin. it can also activate a MAP kinase pathway via β-arrestin in certain contexts.

et al., 2018; Ding et al., 2015).

CXCL12's function in the hippocampus and cortex suggests that it is a protective cytokine that regulates memory and learning ability via the excitability effect of glutamate release from glia in normal conditions (Parachikova and Cotman, 2007; Li et al., 2012). However, in AD, reduced CXCL12/CXCR4 interaction is associated with learning impairment (Trousse et al., 2019; Wang et al., 2022). Moreover, previous studies have shown a notable reduction in CXCL12 signaling can lead cognitive impairment in transgenic AD mouse models(Yan et al., 2022; Lüke et al., 2018). The interaction between CXCL12/CXCR7 decreases CXCL12 levels in the hippocampus, leading to ineffective plaque eradication, more neuronal loss, and cognitive decline(Trousse et al., 2019; Wang et al., 2016).

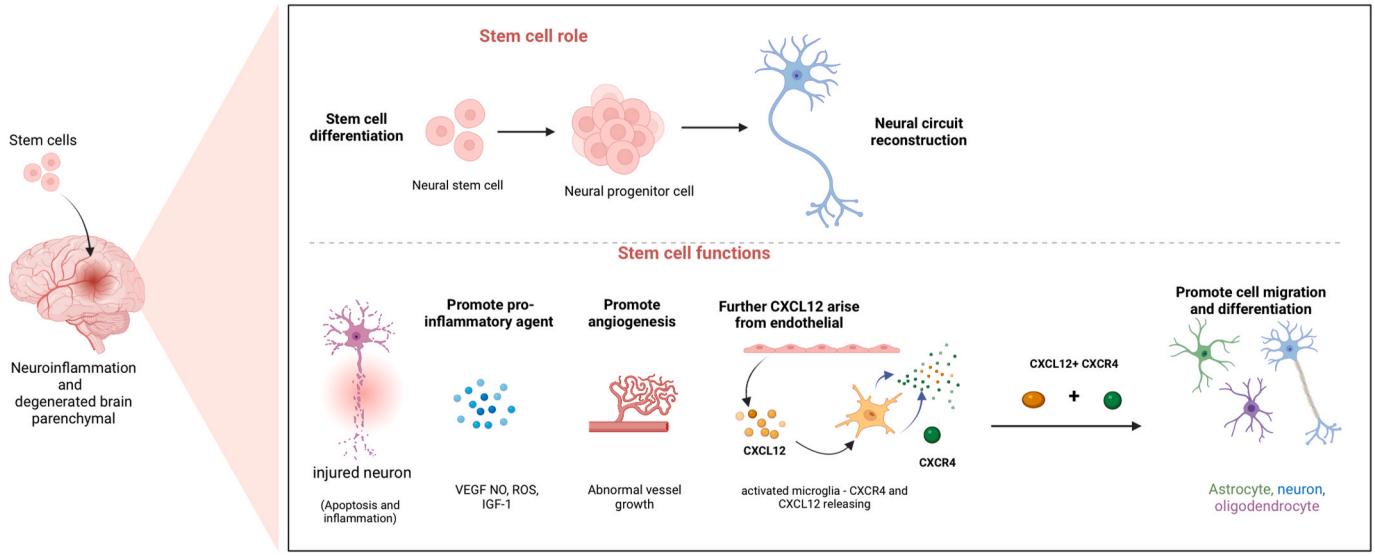

Fig. 3. Stem cell roles and functions in neuroinflammation and regeneration
Neural stem cells naturally stimulate the formation of neural progenitor cells, ultimately resulting in nerve reconstruction. When a nerve sustains an injury or experiences inflammation, pro-inflammatory agents such as: Vascular endothelial growth factor (VEGF), Nitric oxide (NO), Reactive oxygen species (ROS), and Insulin-like Growth Factor 1 (IGF-1) are released from adjacent blood vessels and tissues. These pro-inflammatory agents encourage angiogenesis, leading to enhanced secretion of CXCL12 from surrounding microglial and endothelial cells. As a result, the interaction between CXCL12 and its receptors activates signaling pathways that promote both cell proliferation and migration.

3.1.3. Therapeutic implications and potential interventions

The main target in AD therapeutic strategies is reducing senile plaques and stimulating NPCto replace lost neurons. For eradicating plaques, phagocytic microglial activation via CXCL12/CXCR7 signaling is essential(Luo et al., 2016b). It is important to use Mesenchymal Stem Cells (MSC) to induce neuronal regeneration, but it may bring the risk of abnormal proliferation of other cells and lead to cancers. Thus, targeting immune therapy would result in beneficial outcomes(Lapidot et al., 2005; Ying et al., 2023). (Fig. 3).

Activating microglia has a beneficial effect on eradicating amyloid plaques. Therefore, amplifying the CXCR4/CXCL12 signal transduction by CXCR7 inhibition could be helpful(Trousse et al., 2019; Wang et al., 2022).). Notably, gene manipulation can regulate this axis signaling.

3.1.4. Genetic and epigenetic factors

In the formation of Aβ plaques, certain genes such as ApoE, LPL, TREM-2, and TYObp are overexpressed, resulting in the activation of microglia like DAM(McQuade et al., 2020; McQuade and Blurton-Jones, 2019; Liang et al., 2021). ApoE regulates cholesterol metabolism in astrocytes. As previously known, astrocytes are the main source of cholesterol storage in CNS cells, which supply lipids for other glia. Besides, cholesterol and further lipid metabolism significantly transform signals among neurons in various regards. Mutation in ApoE and other AD-related genes disturbs this process(Kim et al., 2009; Koistinaho et al., 2004). Down-regulated genes through AD are named P2ry-12, CX3Crl, CST3, and CSFLr(McQuade et al., 2020; Wu and Eisel, 2023).

3.2. Parkinson's disease (PD)

3.2.1. PD-associated cognitive decline

PD is a well-known progressive neurodegenerative disorder, involving more than 1% of the 65-year-old and older population(Willis et al., 2022). Cognitive dysfunction is one of the significant symptoms of PD affecting up to 80% of this population. Cognition impairment significantly manifests PD progress from subjective, mild cognitive impairment to dementia. Patients with dementia in PD have deficits in at least two cognitive domains such as executive function, memory, or attention(Aarsland et al., 2021). The risk of developing dementia in PD is reported to be 2/5–6 times higher than in people without PD of similar age (Perez et al., 2012; Aarsland et al., 2001).

The hallmark of PD is the progressive degradation of inhibitory dopaminergic neurons, which project to the nigrostriatal pathway. Dopaminergic neuron degeneration is caused by depositing misfolded neuroprotein called α-synuclein intracellularly and in mitochondria, called Lewy bodies (LB)(Qiao et al., 2012). LB accumulates in various brain regions, including the pars compacta of substantia nigra (SNpc), cortex, hippocampus, and other dopaminergic system areas(Sasikumar and Strafella, 2020).

3.2.2. Role of CXCL12/CXCR4/CXCR7 in PD pathogenesis

In PD, CXCL12 is secreted via microglia under TLR4 (Toll-like Receptor 4)/IκB-α/NF-κB signaling transduction, which initiates an immune response. α-synuclein accumulation triggers microglial activation. TLR4 signaling is enhanced by α-synuclein encounter, and it has an essential role in CXCL12 secretion by microglia in PD(Daniele et al., 2015). Once CXCL12 binds CXCR4, further microglia and other immune cell chemotaxis migration starts by upstreaming FAK (focal adhesion kinase)/Src/Rac1 signaling. Li et al. studies show that the migration and accumulation of immune cells are directed by FAK/Src/Rac1 signal transduction with modulating related-gene expression (Shimoji et al., 2009; Li et al., 2019).

Furthermore, CXCL12 has a pivotal role in regulating dopamine (DA) neurons. This means that when it is in low concentration, it supports dopamine production and release and acts as a neuroprotective agent. At the same time, an excessive gradient promotes neuron destruction by preventing dopamine release(Sánchez-Martín et al., 2013).

On the other hand, CXCL12/CXCR7 interaction can have neuroprotective effects in PD patients, including removing pathologic plaques within dopaminergic neurons, cytokines and other immune agents trafficking from the brain and blood, and aggregating in the hippocampus and cognition-related areas(Aarsland et al., 2021).

3.2.3. Therapeutic strategies targeting the axis

Blocking the CXCL12/CXCR4 axis would be a beneficial therapeutic target for CI-PD-related alleviation. CXCR4 antagonist (AMD3100), TLR4 inhibitor (TAK242), NSC23766 (inhibitor of Rac1), and NF-κB inhibitor (PDTC) are claimed as agents that would be beneficial in PD treatment via preventing CXCL12/CXCR4 signaling pathway recruitment(Li et al., 2019). Meanwhile, based on Kalatskaya et al. studies, AMD3100 may be an allosteric ligand for CXCR7; thus, it can recruit CXCL12/CXCR7 activation(Wang et al., 2018).

3.2.4. Genetic considerations in PD

Single Nucleotide Polymorphisms (SNP) in the human leukocyte antigen (HLA-DRA) gene has a crucial role in microglia activation and following chemokine release (Joers et al., 2017). Other mutations in genes involved in α-synuclein formation are named: (SNCA), ATP13A2, GBA, FBX07, VPS35, PLA2G6, DNAJC6, SYNJ1, UCHL1, parkin (PRKN), LRRK2, PINK1(Srinivasan et al., 2021).

3.3. Multiple Sclerosis (MS)

3.3.1. Cognitive impairment in MS

MS is primarily considered a non-traumatic inflammation-related demyelinating, autoimmune disease affecting the CNS(Comabella and Khoury, 2012; Dobson and Giovannoni, 2019). Cognitive problems are common symptoms of MS that tend to worsen as the disease progresses. They can occur at different stages, affecting the quality of life and bringing socio-economic burden to patients and their caregivers(Brochet and Ruet, 2019; Butler et al., 2022). The prevalence of cognitive impairment in MS varies from 45 to 65% of individuals(Chiaravalloti and DeLuca, 2008). Individuals with relapsing-remitting MS are more prone to cognitive decline than those with clinically isolated syndrome. Cognitive impairment in MS is implicated by reducing information processing speed, visuospatial memory decline, and verbal fluency (Butler et al., 2022).

The primary triggers of MS are external factors such as experiencing long-term anxiety and stress, gender, age between 20s and 40s, Vitamin D deficiency, and environmental stress like prior infection with viruses such as EBV(García-Cuesta et al., 2019; Dobson and Giovannoni, 2019). Following the inflammatory response, proinflammatory cytokines and chemokines are released, attacking the myelin sheaths of white and gray matter neurons(Rocca et al., 2015). Primary destruction occurs via neutrophils and other neuro-inflammatory domains, leading to demyelinated plaque, often at the node of Ranvier. In comparison, macrophage-derived microglia are quiescent at disease onset. The distribution of macrophage-derived T-cells correlates with the disease severity(Yamasaki et al., 2014; Ajami et al., 2011).

3.3.2. CXCL12/CXCR4/CXCR7 axis in MS progression

Through areas with demyelinating plaque, additional chemokines are released by neuroglia to balance altering hemostatic conditions. Under normal conditions, CXCL12 is found in endothelial cells at the luminal surface of BBB and in a few astrocytes. Astrocytes and BBB endothelial cells in the lesion areas of MS express higher levels of CXCL12. IFN-γ and then CXCL12 releasing activate microglia and monocytes. CXCL12 could be an appropriate prognostic and diagnostic biomarker found in CSF of MS patients(Yamasaki et al., 2014; Khoramdelazad et al., 2016).

The increased levels of CXCL12 in MS plaques may contribute to neuronal damage and axonal loss via activating downstream signaling pathways like MAPK, p38 MAPK, PI3K, JAK/STAT, etc. (Zhang et al.,

2009). Several studies showed that redistribution of CXCL12 at BBB is significant in determining the severity of demyelination lesions in MS. The distribution of CXCL12 in active plaques of MS patients shifts from the outer surface to the inner surface of BBB. This change allows other immune cells including CXCR4 to enter CNS, leading to the progression of MS plaques(McCandless et al., 2008).

In experimental autoimmune encephalomyelitis (EAE), ACKR3 (CXCR7) expression in the brain is detected throughout brain vasculature, indicating that ACKR3 likely plays important roles in angiogenesis and maintenance of BBB. Furthermore, elevation of CXCR7 expression on the endothelial barrier and interaction with CXCL12 suggest that it has a crucial role in trafficking leukocytes in CNS and inducing activated microglia(García-Cuesta et al., 2019; Bao et al., 2016).

3.3.3. Therapeutic approaches and remyelination

Basic and primary management of MS should accompany anti-inflammatory medications (Corticosteroids) that suppress HSC-derived inflammation responses. Novel therapeutic strategies have been grounded on the chronicity and severity of the disease. In the acute phase of MS, remyelination is halted because of an extreme amount of inflammation agents, while normal OPCs exist within the active plaque. Hence, CXCL12/CXCR4 signaling has proliferative and migratory properties, restoring CXCL12 at the endothelial barrier recruits OPC in plaques for remyelination(Goldenberg, 2012).

By reducing the activation of CXCL12/CXCR4 through the use of a CXCL12 antibody or CXCR4 antagonists, it is possible to reconstruct normal CXCL12 polarity at the blood-brain barrier (BBB), which is the first step in preventing the worsening of inflammation in active MS. Whereas in the advanced stage, using CXCR7 antagonist (CCX711) can halt the inhibitory effect of CXCR7 on CXCL12/CXCR4-induced OPC proliferation remyelination(Chu et al., 2017; Cruz-Orengo et al., 2011).). According to some studies, synthetic ligands for CXCR7, including VU11207 and VUF11403, have high affinity with CXCR7 as their receptor and elicit β-arrestin pathway individually, then a surface expression of CXCR7 markedly downgrade(Wang et al., 2018; Wijtmans et al., 2012).

The activation of tumor necrosis factor receptor-2 (TNFR2) and the presence of CXCR4 on the membrane of OPC are necessary for remyelination in CNS. TNFR2 activation induces the expression of CXCL12 in demyelinated lesions, particularly in astrocytes, through autocrine signaling. This promotes OPC proliferation and differentiation. Targeting this pathway could be a beneficial treatment strategy for addressing remyelination failure in MS(Patel et al., 2012).

3.3.4. Genetic factors influencing MS and axis function

Several studies show that, in MS patients, TNFR gene mutation induces increasing IFN-γ, activating microglia type1 and following proinflammatory cytokine production(Wheeler et al., 2006). Other gene mutations related to MS include TYK2, ZMIZ-1, CYO27B-1, and HLA-DRB-1 (Dobson and Giovannoni, 2019).

3.4. Amyotrophic Lateral Sclerosis (ALS)

3.4.1. Cognitive aspects of ALS

ALS is a progressive and irreversible disease that eventually induces upper and lower motor neuron loss and muscle atrophy. Histologic studies show ubiquitinated inclusions in the cytoplasm of motor neurons and astrocytes, Bunina bodies (TDP-43), and eosinophilic inclusions in the cytoplasm of motor neurons(Goutman et al., 2022). TDP-43 is a protein that has a significant role in RNA regulation. Also, it is involved in forming stress granules (SGs), which are cytoplasmic components that regulate energy for other parts involving cellular stress response (Neumann et al., 2006; Brettschneider et al., 2012). Cognitive impairment in ALS overlaps with Frontal Lobe Dementia (FLD) pathologically and clinically(Hortobágyi and Cairns, 2018). In ALS, CI is a common symptom associated with the deterioration of the frontal lobe in the late stage of the disease(Brettschneider et al., 2012). Previous studies found a progression of cognitive and behavioral impairment in more than one-third of patients with early-stage ALS by activating microglia and accumulating TDP-43 in motor cortex neurons and prefrontal areas of white matter(Ghaderi et al., 2023; Turner et al., 2004). Along with cognitive deficits in ALS, reduced attention and verbal fluency are more notable.

3.4.2. CXCL12/CXCR4/CXCR7 involvement in ALS pathology

CXCL12 and CXCR4 get upregulated from normal neurons. CXCR7 is expressed in reactive astrocytes and microglia in the late stages of the disease. The overall CXCL12/CXCR4/CXCR7 axis performance in the spinal cord is involved in various processes such as inflammation, oligodendroglia and astrocyte signaling, and neuronal and axonal preservation in sporadic ALS(Andrés-Benito et al., 2020).

CXCL12 and its binding to CXCR4 and CXCR7 receptors is known as a candidate biomarker in sporadic ALS(Lin et al., 2023).

CXCL12 is also involved in forming stress granules, which are cytoplasmic structures that form in response to cellular stress and are involved in mRNA storage and translation regulation(Andrés-Benito et al., 2020). CXCL12 is associated with motor neurons and ALS and a few glial cells in the anterior horn in sporadic ALS. However, the exact role of CXCL12/CXCR4/CXCR7 in ALS pathogenesis is still not fully understood, and further research is needed to elucidate its mechanisms in the disease(Luo et al., 2007).

3.4.3. Potential therapeutic interventions

In ALS, diminished microglial activities would be therapeutic targets. Hence, the CXCR4 antagonist (AMD3100) blocks microglial activities, maintains BBB integrity, and prevents neuronal loss and delayed onset and progression. Parenthetically, downstream of CXCR7 and CXCL12 signaling can alleviate the disease symptoms in the late-stage(McQuade et al., 2020; Wang et al., 2018).

3.4.4. Genetic implications in ALS

TDP-43 genes (TARDBP gene) mutation and other gene alterations associated with the C-terminal domain participate in ALS and related cognitive loss(Suk and Rousseaux, 2020).

4. Comparative analysis, future directions, and conclusion

The CXCL12/CXCR4/CXCR7 axis emerges as a critical player in cognitive impairment across various neurodegenerative diseases, including Alzheimer's, Parkinson's, Multiple Sclerosis, and ALS. While the specific mechanisms vary, several common themes underscore the axis's importance in these disorders.

Neuroinflammation stands out as a key process regulated by this axis across all four diseases. In AD and PD, the axis mediates microglial activation and chemotaxis(Rangaraju et al., 2018; Daniele et al., 2015), while in MS, it contributes to inflammatory responses and demyelination (Rocca et al., 2015). This commonality suggests that modulating the axis could have broad anti-inflammatory effects beneficial in multiple neurodegenerative contexts.

The axis also significantly influences neuronal survival, albeit through disease-specific mechanisms. In AD, it affects amyloid-β accumulation and tau hyperphosphorylation(Gao et al., 2018; Walker, 2020), while in PD, it regulates dopaminergic neuron survival (Sánchez-Martín et al., 2013). In ALS, the axis is involved in motor neuron degeneration(Chiò et al., 2019). These findings highlight the axis's potential as a neuroprotective target across different neurodegenerative pathologies. Synaptic function, crucial for cognitive processes, is another area where the CXCL12/CXCR4/CXCR7 axis plays a vital role. This is particularly evident in AD and PD studies(Parachikova and Cotman, 2007; Zheng et al., 1999; Limatola et al., 2000; Banisadr et al., 2005; Guyon et al., 2005; Li et al., 2012), suggesting that targeting the axis could help maintain cognitive function in these diseases. In MS

and ALS, the axis's role in BBB integrity adds another layer to its importance, influencing disease progression and cognitive outcomes (McCandless et al., 2008; Bao et al., 2016). This aspect opens up potential therapeutic avenues focused on maintaining BBB function.

The identification of axis components, particularly CXCL12, as potential biomarkers across these diseases(Khorramdelazad et al., 2016; Karin, 2010) further underscores its significance and suggests its utility in diagnosis and treatment monitoring. These commonalities have led to several shared therapeutic strategies. CXCR4 antagonists have shown promise across multiple diseases(Li et al., 2019; Wang et al., 2018), while modulation of microglial activity through this axis is a common approach, particularly in AD and PD (Luo et al., 2016b; Li et al., 2019). In MS, strategies targeting this axis aim to promote remyelination (Goldenberg, 2012; Cruz-Orengo et al., 2011), while across all diseases, therapies often aim to provide neuroprotective effects (Lapidot et al., 2005; Sánchez-Martín et al., 2013; Ying et al., 2023). Looking to the future, several exciting research directions emerge. The genetic components identified in each disease(McQuade et al., 2020; McQuade and Blurton-Jones, 2019; Srinivasan et al., 2021) open up possibilities for personalized medicine approaches. Investigating combined therapies that target the CXCL12/CXCR4/CXCR7 axis alongside other treatment modalities could yield more effective interventions. Longitudinal studies are needed to understand the long-term effects of modulating this axis, particularly on cognitive outcomes. Integration of neuroimaging studies with molecular research on this axis could provide new insights into disease progression and treatment efficacy. The potential for targeted therapies is significant. Selective CXCR4 or CXCR7 modulators could fine-tune the axis's activity, while therapies aimed at restoring normal CXCL12 gradients, particularly in MS, show promise(McCandless et al., 2008). Combination therapies targeting both the axis and disease-specific pathologies (e.g., amyloid-β in AD or α-synuclein in PD) represent another exciting avenue. However, several challenges remain. The complexity of the axis, with its intricate interplay between CXCL12, CXCR4, and CXCR7, makes it challenging to predict the full effects of interventions. The heterogeneity of these diseases complicates the development of universally effective treatments. Translating findings from animal models to human patients remains a significant hurdle, and the long-term safety of modulating this axis, which plays roles beyond the CNS, requires careful evaluation. In conclusion, the CXCL12/CXCR4/CXCR7 axis represents a promising target for addressing cognitive impairment in neurodegenerative diseases. Its involvement in neuroinflammation, synaptic function, and neuronal survival across multiple disorders underscores its potential as a therapeutic target. However, the complexity of these signaling pathways necessitates careful consideration in developing interventions. As our understanding of this axis grows, we may uncover new ways to diagnose, treat, and possibly prevent cognitive impairment in neurodegenerative diseases. Future research should focus on elucidating specific mechanisms in each disease, developing targeted therapies, exploring the axis as a potential biomarker, and investigating combination therapies. These efforts could significantly improve the lives of millions affected by these devastating conditions worldwide, offering hope for more effective management of cognitive decline in neurodegenerative diseases.

CRediT authorship contribution statement

Rojin Sarallah: Writing – original draft, Methodology. **Shima Jahani:** Project administration, Methodology, Formal analysis, Data curation. **Alireza Soltani Khaboushan:** Writing – review & editing, Project administration, Conceptualization. **Amir Kian Moaveni:** Methodology, Investigation, Data curation. **Maryam Amiri:** Project administration, Investigation, Formal analysis. **Masoumeh Majidi Zolbin:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ACKR3	Atypical chemokine receptor 3
APP	Amyloid Precursor Protein
Aβ	Amyloid β
BBB	Blood-Brain Barrier
CI	Cognitive Impairment
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CXCL12	Cysteine-X-cysteine chemokine ligand 12
CXCR4	CXC chemokine receptor type 4
CXCR7	CXC chemokine receptor type 7
DA	Dopamine
DAM	Disease-associated microglia
EAE	Experimental Autoimmune Encephalomyelitis
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
FLD	Frontal Lobe Dementia
GABA	γ-aminobutyric acid
GRK	G-protein Receptor Kinase
GSK3	glycogen synthase kinase 3
HSC	Hematopoietic Stem Cell
IFN-γ	Interferon gamma
IGF-1	Insulin-like Growth Factor 1
JAK/STAT	Janus kinase/signal transducers and activators of transcription
LB	Lewy body
MAPK	Mitogen-activated protein kinase
MS	Multiple Sclerosis
NDD	Neurodegenerative Disease
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFT	Neurofibrillary tangle
NK	Natural killer cells
NO	Nitric oxide
NPC	Neural progenitor cell
NSC	Neural stem cell
OPC	Oligodendrocyte progenitor cell
PD	Parkinson's disease
PI3K	Phosphoinositide 3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SDF-1	Stromal cell-derived factor 1
SG	Stress granule
SN	Substantia nigra
SNpc	Substantia nigra pars compacta
TDP-43	TAR DNA-binding protein 43
TLR4	Toll-like Receptor 4
TNF-α	Tumor necrosis factor-α
TNFR2	Tumor necrosis factor receptor-2
VEGF	Vascular endothelial growth factor

Data availability

No data was used for the research described in the article.

References

Aarsland, D., Andersen, K., Larsen, J., Lolk, A., Nielsen, H., Kragh–Sørensen, P., 2001. Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 56 (6), 730–736.

Aarsland, D., Batzu, L., Halliday, G.M., Geurtsen, G.J., Ballard, C., Ray Chaudhuri, K., et al., 2021. Parkinson disease-associated cognitive impairment. Nat. Rev. Dis. Prim. 7 (1), 47.

Ajami, B., Bennett, J.L., Krieger, C., McNagny, K.M., Rossi, F.M., 2011. Infiltrating monocytes trigger EAE progression, but do not contribute to the resident microglia pool. Nat. Neurosci. 14 (9), 1142–1149.

Andrés-Benito, P., Povedano, M., Domínguez, R., Marco, C., Colomina, M.J., López-Pérez, Ó., et al., 2020. Increased CXC motif chemokine ligand 12 levels in cerebrospinal fluid as a candidate biomarker in sporadic amyotrophic lateral sclerosis. Int. J. Mol. Sci. 21 (22), 8680.

Banisadr, G., Rostène, W., Kitabgi, P., Parsadaniantz, S.M., 2005. Chemokines and brain functions. Curr. Drug Targets - Inflamm. Allergy 4 (3), 387–399.

Banisadr, G., Podojil, J.R., Miller, S.D., Miller, R.J., 2016. Pattern of CXCR7 gene expression in mouse brain under normal and inflammatory conditions. J. Neuroimmune Pharmacol. 11, 26–35.

Bao, J., Zhu, J., Luo, S., Cheng, Y., Zhou, S., 2016. CXCR7 suppression modulates microglial chemotaxis to ameliorate experimentally-induced autoimmune encephalomyelitis. Biochem. Biophys. Res. Commun. 469 (1), 1–7.

Bonavia, R., Bajetto, A., Barbero, S., Pirani, P., Florio, T., Schettini, G., 2003. Chemokines and their receptors in the CNS: expression of CXCL12/SDF-1 and CXCR4 and their role in astrocyte proliferation. Toxicol. Lett. 139 (2–3), 181–189.

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., 1999. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur. Arch. Psychiatr. Clin. Neurosci. 249, S14–S22.

Brettschneider, J., Libon, D.J., Toledo, J.B., Xie, S.X., McCluskey, L., Elman, L., et al., 2012. Microglial activation and TDP-43 pathology correlate with executive dysfunction in amyotrophic lateral sclerosis. Acta Neuropathol. 123, 395–407.

Brochet, B., Ruet, A., 2019. Cognitive impairment in multiple sclerosis with regards to disease duration and clinical phenotypes. Front. Neurol. 10, 261.

Butler, Pagnotti R., Hua, L.H., Miller, J.B., 2022. Cognition and disease characteristics in adult onset versus late onset multiple sclerosis. Multiple Sclerosis Journal 28 (6), 933–941.

Carbajal, K.S., Miranda, J.L., Tsukamoto, M.R., Lane, T.E., 2011. CXCR4 signaling regulates remyelination by endogenous oligodendrocyte progenitor cells in a viral model of demyelination. Glia 59 (12), 1813–1821.

Chen, J.X., Yan, S.S., 2010. Role of mitochondrial amyloid-β in Alzheimer's disease. J. Alzheim. Dis. 20 (s2), S569–S578.

Cheng, X., Wang, H., Zhang, X., Zhao, S., Zhou, Z., Mu, X., et al., 2017. The role of SDF-1/CXCR4/CXCR7 in neuronal regeneration after cerebral ischemia. Front. Neurosci. 11, 590.

Chiaravalloti, N.D., DeLuca, J., 2008. Cognitive impairment in multiple sclerosis. Lancet Neurol. 7 (12), 1139–1151.

Chiò, A., Moglia, C., Canosa, A., Manera, U., Vasta, R., Brunetti, M., et al., 2019. Cognitive impairment across ALS clinical stages in a population-based cohort. Neurology 93 (10), e984–e994.

Chu, T., Shields, L.B., Zhang, Y.P., Feng, S.-Q., Shields, C.B., Cai, J., 2017. CXCL12/CXCR4/CXCR7 chemokine axis in the central nervous system: therapeutic targets for remyelination in demyelinating diseases. Neuroscientist 23 (6), 627–648.

Comabella, M., Khoury, S.J., 2012. Immunopathogenesis of multiple sclerosis. Clin. Immunol. 142 (1), 2–8.

Cruz-Orengo, L., Holman, D.W., Dorsey, D., Zhou, L., Zhang, P., Wright, M., et al., 2011. CXCR7 influences leukocyte entry into the CNS parenchyma by controlling abluminal CXCL12 abundance during autoimmunity. J. Exp. Med. 208 (2), 327–339.

Daniele, S.G., Béraud, D., Davenport, C., Cheng, K., Yin, H., Maguire-Zeiss, K.A., 2015. Activation of MyD88-dependent TLR1/2 signaling by misfolded α-synuclein, a protein linked to neurodegenerative disorders. Sci. Signal. 8 (376), ra45–ra.

de Bock, C.E., Cools, J., 2015. T-ALL: home is where the CXCL12 is. Cancer Cell 27 (6), 745–746.

Deczkowska, A., Keren-Shaul, H., Weiner, A., Colonna, M., Schwartz, M., Amit, I., 2018. Disease-associated microglia: a universal immune sensor of neurodegeneration. Cell 173 (5), 1073–1081.

Ding, W., Ding, L., Li, F., Han, Y., Mu, L., 2015. Neurodegeneration and cognition in Parkinson's disease: a review. Eur. Rev. Med. Pharmacol. Sci. 19 (12), 2275–2281.

Dobson, R., Giovannoni, G., 2019. Multiple sclerosis–a review. Eur. J. Neurol. 26 (1), 27–40.

Dziembowska, M., Tham, T., Lau, P., Vitry, S., Lazarini, F., Dubois-Dalcq, M., 2005. A role for CXCR4 signaling in survival and migration of neural and oligodendrocyte precursors. Glia 50 (3), 258–269.

Engelhardt, B., Ransohoff, R.M., 2012. Capture, crawl, cross: the T cell code to breach the blood–brain barriers. Trends Immunol. 33 (12), 579–589.

Gao, Y., Tan, L., Yu, J.-T., Tan, L., 2018. Tau in Alzheimer's disease: mechanisms and therapeutic strategies. Curr. Alzheimer Res. 15 (3), 283–300.

García-Cuesta, E.M., Santiago, C.A., Vallejo-Díaz, J., Juarranz, Y., Rodríguez-Frade, J.M., Mellado, M., 2019. The role of the CXCL12/CXCR4/ACKR3 axis in autoimmune diseases. Front. Endocrinol. 10, 585.

Ghaderi, S., Fatehi, F., Kalra, S., Batouli, S.A.H., 2023. MRI biomarkers for memory-related impairment in amyotrophic lateral sclerosis: a systematic review. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 1–17.

Giannakopoulos, P., Gold, G., von Gunten, A., Hof, P.R., Bouras, C., 2009. Pathological substrates of cognitive decline in Alzheimer's disease. Dementia in clinical practice 24, 20–29.

Goldenberg, M.M., 2012. Multiple sclerosis review. Pharmacy and therapeutics 37 (3), 175.

Gonzales, M.M., Garbarino, V.R., Pollet, E., Palavicini, J.P., Kellogg, D.L., Kraig, E., et al., 2022. Biological aging processes underlying cognitive decline and neurodegenerative disease. J. Clin. Invest. 132 (10).

Goutman, S.A., Hardiman, O., Al-Chalabi, A., Chió, A., Savelieff, M.G., Kiernan, M.C., et al., 2022. Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. Lancet Neurol. 21 (5), 465–479.

Guyon, A., 2014. CXCL12 chemokine and its receptors as major players in the interactions between immune and nervous systems. Front. Cell. Neurosci. 8, 65.

Guyon, A., Banisadr, G., Rovere, C., Cervantes, A., Kitabgi, P., Melik-Parsadaniantz, S., et al., 2005. Complex effects of stromal cell-derived factor-1α on melanin-concentrating hormone neuron excitability. Eur. J. Neurosci. 21 (3), 701–710.

Guyon, A., Kussrow, A., Olmsted, I.R., Sandoz, G., Bornhop, D.J., Nahon, J.-L., 2013. Baclofen and other GABAB receptor agents are allosteric modulators of the CXCL12 chemokine receptor CXCR4. J. Neurosci. 33 (28), 11643–11654.

Heinisch, S., Kirby, L.G., 2010. SDF-1α/CXCL12 enhances GABA and glutamate synaptic activity at serotonin neurons in the rat dorsal raphe nucleus. Neuropharmacology 58 (2), 501–514.

Hortobágyi, T., Cairns, N.J., 2018. Amyotrophic lateral sclerosis and non-tau frontotemporal lobar degeneration. Handb. Clin. Neurol. 145, 369–381.

Huynh, C., Dingemanse, J., Zu Schwabedissen, H.E.M., Sidharta, P.N., 2020. Relevance of the CXCR4/CXCR7-CXCL12 axis and its effect in pathophysiological conditions. Pharmacol. Res. 161, 105092.

Joers, V., Tansey, M.G., Mulas, G., Carta, A.R., 2017. Microglial phenotypes in Parkinson's disease and animal models of the disease. Prog. Neurobiol. 155, 57–75.

Karin, N., 2010. The multiple faces of CXCL12 (SDF-1α) in the regulation of immunity during health and disease. J. Leukoc. Biol. 88 (3), 463–473.

Kelley, B.J., Petersen, R.C., 2007. Alzheimer's disease and mild cognitive impairment. Neurol. Clin. 25 (3), 577–609.

Khorramdelazad, H., Bagheri, V., Hassanshahi, G., Zeinali, M., Vakilian, A., 2016. New insights into the role of stromal cell-derived factor 1 (SDF-1/CXCL12) in the pathophysiology of multiple sclerosis. J. Neuroimmunol. 290, 70–75.

Kim, J., Basak, J.M., Holtzman, D.M., 2009. The role of apolipoprotein E in Alzheimer's disease. Neuron 63 (3), 287–303.

Koistinaho, M., Lin, S., Wu, X., Esterman, M., Koger, D., Hanson, J., et al., 2004. Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-β peptides. Nat. Med. 10 (7), 719–726.

Lapidot, T., Dar, A., Kollet, O., 2005. How do stem cells find their way home? Blood 106 (6), 1901–1910.

Lauro, C., Limatola, C., 2020. Metabolic reprograming of microglia in the regulation of the innate inflammatory response. Front. Immunol. 11, 493.

Levoye, A., Balabanian, K., Baleux, F., Bachelerie, F., Lagane, B., 2009. CXCR7 heterodimerizes with CXCR4 and regulates CXCL12-mediated G protein signaling. Blood, The Journal of the American Society of Hematology 113 (24), 6085–6093.

Li, M., Hale, J.S., Rich, J.N., Ransohoff, R.M., Lathia, J.D., 2012. Chemokine CXCL12 in neurodegenerative diseases: an SOS signal for stem cell-based repair. Trends Neurosci. 35 (10), 619–628.

Li, Y., Niu, M., Zhao, A., Kang, W., Chen, Z., Luo, N., et al., 2019. CXCL12 is involved in α-synuclein-triggered neuroinflammation of Parkinson's disease. J. Neuroinflammation 16 (1), 1–14.

Liang, X., Wu, H., Colt, M., Guo, X., Pluimer, B., Zeng, J., et al., 2021. Microglia and its genetics in Alzheimer's disease. Curr. Alzheimer Res. 18 (9), 676.

Limatola, C., Giovannelli, A., Maggi, L., Ragozzino, D., Castellani, L., Ciotti, M.T., et al., 2000. SDF-1α-mediated modulation of synaptic transmission in rat cerebellum. Eur. J. Neurosci. 12 (7), 2497–2504.

Lin, D., Liu, H., Song, H., Chen, B., Fu, J., Sun, M., et al., 2023. Upregulation of CXC motif chemokine 12 in the spinal cord alleviated the symptoms of experimental autoimmune encephalomyelitis in Lewis rats. Front. Neurosci. 17, 1105530.

Lindeboom, J., Weinstein, H., 2004. Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. Eur. J. Pharmacol. 490 (1–3), 83–86.

Long, H.-Z., Cheng, Y., Zhou, Z.-W., Luo, H.-Y., Wen, D.-D., Gao, L.-C., 2021. PI3K/AKT signal pathway: a target of natural products in the prevention and treatment of Alzheimer's disease and Parkinson's disease. Front. Pharmacol. 12, 648636.

Lüke, F., Blazquez, R., Yamaci, R.F., Lu, X., Pregler, B., Hannus, S., et al., 2018. Isolated metastasis of an EGFR-L858R-mutated NSCLC of the meninges: the potential impact of CXCL12/CXCR4 axis in EGFRmut NSCLC in diagnosis, follow-up and treatment. Oncotarget 9 (27), 18844.

Luo, Y., Xue, H., Pardo, A.C., Mattson, M.P., Rao, M.S., Maragakis, N.J., 2007. Impaired SDF1/CXCR4 signaling in glial progenitors derived from SOD1G93A mice. J. Neurosci. Res. 85 (11), 2422–2432.

Luo, X., Tai, W.L., Sun, L., Pan, Z., Xia, Z., Chung, S.K., et al., 2016a. Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain. Mol. Pain 12, 1744806916636385.

Luo, X., Wang, X., Xia, Z., Chung, S.K., Cheung, C.W., 2016b. CXCL12/CXCR4 axis: an emerging neuromodulator in pathological pain. Rev. Neurosci. 27 (1), 83–92.

Matsuda, S., Ikeda, Y., Murakami, M., Nakagawa, Y., Tsuji, A., Kitagishi, Y., 2019. Roles of PI3K/AKT/GSK3 pathway involved in psychiatric illnesses. Diseases 7 (1), 22.

McCandless, E.E., Piccio, L., Woerner, B.M., Schmidt, R.E., Rubin, J.B., Cross, A.H., et al., 2008. Pathological expression of CXCL12 at the blood-brain barrier correlates with severity of multiple sclerosis. Am. J. Pathol. 172 (3), 799–808.

McDonald, W.M., 2017. Overview of neurocognitive disorders. Focus 15 (1), 4–12.

McQuade, A., Blurton-Jones, M., 2019. Microglia in Alzheimer's disease: exploring how genetics and phenotype influence risk. J. Mol. Biol. 431 (9), 1805–1817.

McQuade, A., Kang, Y.J., Hasselmann, J., Jairaman, A., Sotelo, A., Coburn, M., et al., 2020. Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. Nat. Commun. 11 (1), 5370.
Mithal, D.S., Banisadr, G., Miller, R.J., 2012. CXCL12 signaling in the development of the nervous system. J. Neuroimmune Pharmacol. 7, 820–834.
Muzio, L., Viotti, A., Martino, G., 2021. Microglia in neuroinflammation and neurodegeneration: from understanding to therapy. Front. Neurosci. 15, 742065.
Nelson, P.T., Alafuzoff, I., Bigio, E.H., Bouras, C., Braak, H., Cairns, N.J., et al., 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol. 71 (5), 362–381.
Neumann, M., Sampathu, D.M., Kwong, L.K., Truax, A.C., Micsenyi, M.C., Chou, T.T., et al., 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314 (5796), 130–133.
Parachikova, A., Cotman, C.W., 2007. Reduced CXCL12/CXCR4 results in impaired learning and is downregulated in a mouse model of Alzheimer disease. Neurobiol. Dis. 28 (2), 143–153.
Patel, J.R., Williams, J.L., Muccigrosso, M.M., Liu, L., Sun, T., Rubin, J.B., et al., 2012. Astrocyte TNFR2 is required for CXCL12-mediated regulation of oligodendrocyte progenitor proliferation and differentiation within the adult CNS. Acta Neuropathol. 124, 847–860.
Perez, F., Helmer, C., Foubert-Samier, A., Auriacombe, S., Dartigues, J.-F., Tison, F., 2012. Risk of dementia in an elderly population of Parkinson's disease patients: a 15-year population-based study. Alzheimer's Dementia 8 (6), 463–469.
Qiao, S., Luo, J., Jin, J., 2012. Role of microglial activation induced by α-synuclein in pathogenesis of Parkinson's disease. Zhejiang da xue xue bao Yi xue ban= Journal of Zhejiang University Medical Sciences 41 (2), 210–214.
Qu, Y., Mao, M., Li, X., Zhang, L., Huang, X., Yang, C., et al., 2008. Enhanced migration and CXCR4 over-expression in fibroblasts with telomerase reconstitution. Mol. Cell. Biochem. 313, 45–52.
Rangaraju, S., Dammer, E.B., Raza, S.A., Rathakrishnan, P., Xiao, H., Gao, T., et al., 2018. Identification and therapeutic modulation of a pro-inflammatory subset of disease-associated-microglia in Alzheimer's disease. Mol. Neurodegener. 13, 1–25.
Reaux-Le Goazigo, A., Rivat, C., Kitabgi, P., Pohl, M., Melik, Parsadaniantz S., 2012. Cellular and subcellular localization of CXCL12 and CXCR4 in rat nociceptive structures: physiological relevance. Eur. J. Neurosci. 36 (5), 2619–2631.
Rocca, M.A., Amato, M.P., De Stefano, N., Enzinger, C., Geurts, J.J., Penner, I.-K., et al., 2015. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. Lancet Neurol. 14 (3), 302–317.
Rothhammer, V., Borucki, D.M., Tjon, E.C., Takenaka, M.C., Chao, C.-C., Ardura-Fabregat, A., et al., 2018. Microglial control of astrocytes in response to microbial metabolites. Nature 557 (7707), 724–728.
Sánchez-Alcañiz, J.A., Haege, S., Mueller, W., Pla, R., Mackay, F., Schulz, S., et al., 2011. Cxcr7 controls neuronal migration by regulating chemokine responsiveness. Neuron 69 (1), 77–90.
Sánchez-Martín, L., Sánchez-Mateos, P., Cabañas, C., 2013. CXCR7 impact on CXCL12 biology and disease. Trends Mol. Med. 19 (1), 12–22.
Santagata, S., Ieranò, C., Trotta, A.M., Capiluongo, A., Auletta, F., Guardascione, G., et al., 2021. CXCR4 and CXCR7 signaling pathways: a focus on the cross-talk between cancer cells and tumor microenvironment. Front. Oncol. 11, 591386.
Sarailoo, M., Afshari, S., Asghariazar, V., Safarzadeh, E., Dadkhah, M., 2022. Cognitive impairment and neurodegenerative diseases development associated with organophosphate pesticides exposure: a review study. Neurotox. Res. 40 (5), 1624–1643.
Sasikumar, S., Strafella, A.P., 2020. Imaging mild cognitive impairment and dementia in Parkinson's disease. Front. Neurol. 11, 47.
Shi, Y., Riese, D.J., Shen, J., 2020. The role of the CXCL12/CXCR4/CXCR7 chemokine axis in cancer. Front. Pharmacol. 11, 574667.
Shimizu, S., Brown, M., Sengupta, R., Penfold, M.E., Meucci, O., 2011. CXCR7 protein expression in human adult brain and differentiated neurons. PLoS One 6 (5), e20680.
Shimoji, M., Pagan, F., Healton, E.B., Mocchetti, I., 2009. CXCR4 and CXCL12 expression is increased in the nigro-striatal system of Parkinson's disease. Neurotox. Res. 16, 318–328.
Si, M., Song, Y., Wang, X., Wang, D., Liu, X., Qu, X., et al., 2022. CXCL12/CXCR7/β-arrestin1 biased signal promotes epithelial-to-mesenchymal transition of colorectal cancer by repressing miRNAs through YAP1 nuclear translocation. Cell Biosci. 12 (1), 1–21.
Srinivasan, E., Chandrasekhar, G., Chandrasekar, P., Anbarasu, K., Vickram, A., Karunakaran, R., et al., 2021. Alpha-synuclein aggregation in Parkinson's disease. Front. Med. 8, 736978.
Subhramanyam, C.S., Wang, C., Hu, Q., Dheen, S.T. (Eds.), 2019. Microglia-mediated Neuroinflammation in Neurodegenerative Diseases. Seminars in Cell & Developmental Biology. Elsevier.
Sugiyama, M.G., Fairn, G.D., Antonescu, C.N., 2019. Akt-ing up just about everywhere: compartment-specific Akt activation and function in receptor tyrosine kinase signaling. Front. Cell Dev. Biol. 7, 70.
Suk, T.R., Rousseaux, M.W., 2020. The role of TDP-43 mislocalization in amyotrophic lateral sclerosis. Mol. Neurodegener. 15, 1–16.
Terheyden-Keighley, D., Hilla, A.M., Fischer, D., 2022. CXCR4 signaling in central nervous system regeneration: friend or foe? Neural Regeneration Research 17 (7), 1481.
Tiwari, S., Atluri, V., Kaushik, A., Yndart, A., Nair, M., 2019. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int. J. Nanomed. 5541–5554.
Trousse, F., Jemli, A., Silhol, M., Garrido, E., Crouzier, L., Naert, G., et al., 2019. Knockdown of the CXCL12/CXCR7 chemokine pathway results in learning deficits and neural progenitor maturation impairment in mice. Brain Behav. Immun. 80, 697–710.
Turner, M., Cagnin, A., Turkheimer, F., Miller, C., Shaw, C., Brooks, D., et al., 2004. Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study. Neurobiol. Dis. 15 (3), 601–609.
Walker, L.C., 2020. Aβ plaques. Free neuropathology 1.
Wang, Y., Xu, P., Qiu, L., Zhang, M., Huang, Y., Zheng, J.C., 2016. CXCR7 participates in CXCL12-mediated cell cycle and proliferation regulation in mouse neural progenitor cells. Curr. Mol. Med. 16 (8), 738–746.
Wang, C., Chen, W., Shen, J., 2018. CXCR7 targeting and its major disease relevance. Front. Pharmacol. 9, 641.
Wang, Q.L., Fang, C.L., Huang, X.Y., Xue, L.L., 2022. Research progress of the CXCR4 mechanism in Alzheimer's disease. Ibrain 8 (1), 3–14.
Wheeler, R.D., Zehntner, S.P., Kelly, L.M., Bourbonnière, L., Owens, T., 2006. Elevated interferon gamma expression in the central nervous system of tumour necrosis factor receptor 1-deficient mice with experimental autoimmune encephalomyelitis. Immunology 118 (4), 527–538.
Wijtmans, M., Maussang, D., Sirci, F., Scholten, D.J., Canals, M., Mujić-Delić, A., et al., 2012. Synthesis, modeling and functional activity of substituted styrene-amides as small-molecule CXCR7 agonists. Eur. J. Med. Chem. 51, 184–192.
Williams, J.L., Holman, D.W., Klein, R.S., 2014. Chemokines in the balance: maintenance of homeostasis and protection at CNS barriers. Front. Cell. Neurosci. 8, 154.
Willis, A., Roberts, E., Beck, J., Fiske, B., Ross, W., Savica, R., et al., 2022. Incidence of Parkinson disease in North America. npj Parkinson's Disease 8 (1), 170.
Wilson, R.S., Segawa, E., Boyle, P.A., Anagnos, S.E., Hizel, L.P., Bennett, D.A., 2012. The natural history of cognitive decline in Alzheimer's disease. Psychol. Aging 27 (4), 1008.
Wu, Y., Eisel, U.L., 2023. Microglia-astrocyte communication in alzheimer's disease. J. Alzheim. Dis. (Preprint), 1–19.
Xiang, Y., Li, Y., Zhang, Z., Cui, K., Wang, S., Yuan, X-b, et al., 2002. Nerve growth cone guidance mediated by G protein–coupled receptors. Nat. Neurosci. 5 (9), 843–848.
Yamasaki, R., Lu, H., Butovsky, O., Ohno, N., Rietsch, A.M., Cialic, R., et al., 2014. Differential roles of microglia and monocytes in the inflamed central nervous system. J. Exp. Med. 211 (8), 1533–1549.
Yan, Y., Su, J., Zhang, Z., 2022. The CXCL12/CXCR4/ACKR3 response axis in chronic neurodegenerative disorders of the central nervous system: therapeutic target and biomarker. Cell. Mol. Neurobiol. 42 (7), 2147–2156.
Ying, C., Zhang, J., Zhang, H., Gao, S., Guo, X., Lin, J., et al., 2023. Stem cells in central nervous system diseases: promising therapeutic strategies. Exp. Neurol., 114543
Zabel, B.A., Wang, Y., Lewén, S., Berahovich, R.D., Penfold, M.E., Zhang, P., et al., 2009. Elucidation of CXCR7-mediated signaling events and inhibition of CXCR4-mediated tumor cell transendothelial migration by CXCR7 ligands. J. Immunol. 183 (5), 3204–3211.
Zella, M.A.S., Metzdorf, J., Ostendorf, F., Maass, F., Muhlack, S., Gold, R., et al., 2019. Novel immunotherapeutic approaches to target alpha-synuclein and related neuroinflammation in Parkinson's disease. Cells 8 (2), 105.
Zhang, Y., Argaw, A.T., Gurfein, B.T., Zameer, A., Snyder, B.J., Ge, C., et al., 2009. Notch1 signaling plays a role in regulating precursor differentiation during CNS remyelination. Proc. Natl. Acad. Sci. USA 106 (45), 19162–19167.
Zheng, J., Thylin, M.R., Ghorpade, A., Xiong, H., Persidsky, Y., Cotter, R., et al., 1999. Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic mechanisms of HIV-1-associated dementia. J. Neuroimmunol. 98 (2), 185–200.
Zilkha-Falb, R., Kaushansky, N., Kawakami, N., Ben-Nun, A., 2016. Post-CNS-inflammation expression of CXCL12 promotes the endogenous myelin/neuronal repair capacity following spontaneous recovery from multiple sclerosis-like disease. J. Neuroinflammation 13 (1), 1–19.
Zlotnik, A., Yoshie, O., 2000. Chemokines: a new classification system and their role in immunity. Immunity 12 (2), 121–127.