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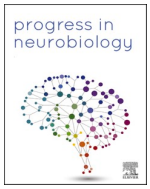

The multifaceted role of the CXC chemokines and receptors signaling axes in ALS pathophysiology

Valentina La Cognata, Giovanna Morello, Maria Guarnaccia, Sebastiano Cavallaro *

Institute for Biomedical Research and Innovation, National Research Council, Via P. Gaifami 18, Catania 95126, Italy

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a late-onset motor neuron disease with complex genetic basis and still no clear etiology. Multiple intertwined layers of immune system-related dysfunctions and neuroinflammatory mechanisms are emerging as substantial determinants in ALS onset and progression. In this review, we collect the increasingly arising evidence implicating four main CXC chemokines/cognate receptors signaling axes (CXCR1/2-CXCL1/2/8; CXCR3-CXCL9/10/11; CXCR4/7-CXCL12; CXCR5-CXCL13) in the pathophysiology of ALS. Findings in preclinical models implicate these signaling pathways in motor neuron toxicity and neuroprotection, while in ALS patients dysregulation of CXCLs/CXCRs has been shown at both central and peripheral levels. Immunological monitoring of CXC-ligands in ALS may allow tracking of disease progression, while pharmacological modulation of CXC-receptors provides a novel therapeutic strategy. A deeper understanding of the interplay between CXC-mediated neuroinflammation and ALS is crucial to advance research into treatments for this debilitating uncurable disorder.

1. Background

Amyotrophic lateral sclerosis (ALS) is an incurable heterogenous neurodegenerative disorder characterized by the combined depletion of cortical, bulbar and spinal motor neurons, resulting in rapidly progressive paralysis and respiratory insufficiency within three to five years after the symptoms begin (Brenner and Freischmidt, 2022; Smukowski et al., 2022). The clinical course varies widely with phenotypic variability involving several clinical aspects, such as site and age of onset, rate of progression and response to therapy (Thomson et al., 2023). About 5–10% of patients are familial ALS (fALS) cases, defined by more than one family member affected and linked to disease-causing mutations, while the great majority (85–90% cases) are sporadic ALS (sALS) patients probably associated to a polygenic and multifactorial etiology (Mathis et al., 2019; Gentile et al., 2022, 2021). Besides symptomatic and palliative care treatments, only few therapeutic options exist in ALS, with riluzole still being the reference drug improving survival of a few months (Johnson et al., 2022; Turner et al., 2001).

During the past years, a rapidly increasing number of multiple biological processes have been linked to ALS, including RNA processing, excitotoxicity, oxidative stress, cytoskeletal abnormalities, impaired axonal transport, mitochondrial dysfunction and protein aggregation (Morello et al., 2018; La Cognata et al., 2020), but the causes underlying ALS remain to be fully elucidated. Accumulating evidence are indicating both the immune system response and the neuroinflammatory mechanisms as crucial ALS determinants (Beland et al., 2020). Data supporting T cells infiltration, glial activation and astrogliosis in affected patients are copious, and multiple intertwined levels of immune system-related dysfunctions exist, counting chronic pro-inflammation states, autoimmunity conditions and inefficient response, likely generating an imbalance between immune-mediated neuroprotection and neurotoxicity (Beland et al., 2020). Furthermore, activated immune cells are summoned in both the peripheral- and central-nervous system, but the crosstalk between the peripheral immune system and central resident immune cells has not been well defined (Yu et al., 2022).

Among the wide plethora of cellular and molecular players implicated in the immunological response processes, chemokines that promote chemokinesis (Greek—kinos, movement), are known to be crucial contributing factors since they are involved in a variety of pathophysiological processes and control both directly or indirectly several inflammatory and immunological signaling events (Wu et al., 2022). Chemokines are a large family of small highly conserved proteins playing a chief role in the regulation of migratory patterns of immune and inflammatory mediators throughout the body. They are expressed

* Corresponding author.
E-mail address: sebastiano.cavallaro@cnr.it (S. Cavallaro).

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both at peripheral and central level, and participate in embryogenesis, angiogenesis, hematopoiesis, apoptosis, mitosis, as well as in central nervous system functions, such as neuronal development, synaptic transmission and disease-associated neuroinflammation (de Haas et al., 2007; Savarin-Vuaillat and Ransohoff, 2007; Cavallaro, 2013). Based on the arrangement of the N-terminal two cysteine residues, chemokines are classified into four different subfamilies (CC, CXC, CX3C and XC). In the CC chemokines, two of the first four conserved cysteines are adjacent to each other, while the CXC chemokines have a single variable non-conserved amino acid between them. CX3C chemokines have three variable amino acids between the two conserved cysteines, while XC chemokines lack the first and third cysteines of the motif and have a single variable cysteine residue in the amino terminus (Wu et al., 2022; Komolafe and Pacurari, 2022). To date, more than 50 chemokines have been identified in various cell types and tissues, with the CC and CXC chemokines being the most numerous. The multifaceted functions of chemokines in multicellular organisms are orchestrated by their seven transmembrane or serpentine G protein-coupled receptors (GPCRs), which are classified as CC, CXC, CX3C, or XC, according to the subfamily of their ligands (Wu et al., 2022; Komolafe and Pacurari, 2022).

To date, great efforts have been made to understand the roles of both chemokines and related receptors in ALS pathophysiology. Here, we will focus on CXC chemokines and describe recent findings regarding their contribution in ALS onset and progression, as well as their modulation therapy against this fatal neurodegenerative disease.

2. The CXCL/CXCR signaling axes

In addition to the CXC cysteine motif (Wu et al., 2022; Komolafe and Pacurari, 2022), the CXC chemokine subfamily is further subdivided into two main classes depending on the presence or absence of a Glu-Leu-Arg (ELR) motif in the NH_2-terminus (ELR^+ members and ELR^- members). The ELR^+ members (CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8) have significant neutrophil chemotactic and activating characteristics, while the ELR^- members (CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL16) exert no chemotactic effects on neutrophils but rather act primarily on mononuclear leukocytes, including activated/memory T cells and natural killer cells (Fig. 1) (Wu et al., 2022; Komolafe and Pacurari, 2022).

CXC chemokines, like other types of chemokines, work by interacting with their corresponding receptors (CXCR1 to CXCR7) on the surface of cells, particularly leukocytes. These receptors can be activated by one (monogamous receptors) or more endogenous chemokines (promiscuous receptors) (Nagata et al., 2022). The ELR^+ CXCLs are ligands for CXCR1 and/or CXCR2, while the ELR^- CXCLs are primarily the ligands for CXCR3, CXCR4, CXCR5, CXCR6 or CXCR7 (Fig. 1) (Wu et al., 2022; Komolafe and Pacurari, 2022). Upon binding with the endogenous ligand, the receptor undergoes conformational changes that culminate in exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP) with the consequent activation of differential intracellular signaling pathways and calcium mobilization. A few of the CXCRs are atypical receptors, which are not coupled to a G protein but to ß-arrestins, including the atypical chemokine receptor 3 (ACKR3) also known as CXCR7 (Cabrero-de Las Heras and Martinez-Balibrea, 2018). The response elicited by a given chemokine ligand is determined by the chemokine's cellular location as well as the type of cognate receptor to which it binds (Wu et al., 2022; Komolafe and Pacurari, 2022).

In the next paragraphs we will review the current emerging evidence implicating CXC chemokines and cognate receptors in ALS, and highlight their usefulness as monitoring disease-biomarkers or drug targets for therapeutic intervention.

3. The role and therapeutic relevance of CXC motif chemokines and cognate receptors in ALS

3.1. CXCR1/2 - CXCL1/2/8 axis

CXCR1/2 (formerly termed IL-8 receptor alpha and beta) consist in 7 transmembrane domains, an N-terminal mainly responsible for binding extracellular chemokines and a C-terminal responsible for receiving and transmitting information downstream (Jiang et al., 2023; Sitaru et al., 2023). They are mainly expressed on neutrophils, macrophages, mast cells or other leukocytes and mediate neutrophilic granulocytes recruitment, thus playing a major role in the pathophysiology of a wide spectrum of inflammatory conditions (Sitaru et al., 2023). In the central nervous system, CXCR2 is expressed in cortical neurons, hippocampus, cerebellum (Horuk et al., 1997), motor cortex neurons (De Paola et al., 2007; La Cognata et al., 2021a), and spinal cord ventral horns (La Cognata et al., 2023), where participates in neuroinflammatory mechanisms and promotes macrophage and neutrophil infiltration into the site of damage in response to endogenous ligands release (Jiang et al., 2023; Veenstra and Ransohoff, 2012; Semple et al., 2010; Ha et al., 2017).

CXCR1 and CXCR2 have 77% amino acid sequence homology, and their activation is carried out by binding with different affinity to multiple ELR^+ CXC motif chemokines (CXCL1 to CXCL8). In humans, the main ligand is the Interleukin-8 (CXCL8/IL-8), which represents the primary neutrophils-chemoattractant during both acute and chronic inflammation. In mice and rats, no homologue of human CXCL8 has been described, but CXCL1 (also called keratinocyte-derived chemokine/KC/Groα) and CXCL2 (or macrophage inflammatory protein 2-alpha, MIP2α) are considered the functional homologues of CXCL8 (Konrad and Reutershan, 2012).

Mounting experimental evidence from multiple studies pointed to an essential role of CXCR1/2-CXCL1/2/8 axis in ALS pathophysiology (Semple et al., 2010; Zhang et al., 2017). ALS patients from multiple

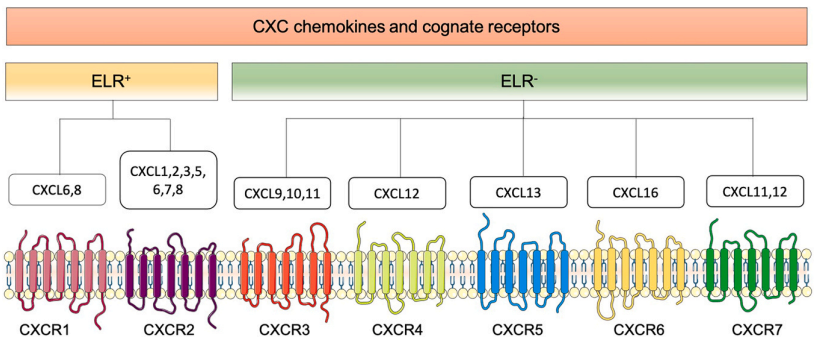

Fig. 1. Classification of CXC chemokines and their cognate receptors. The CXC chemokine family is divided into two subtypes: ELR^+ members and ELR^- members. ELR^+ members are endogenous ligands of CXCR1/2, while ELR^- members bind to CXCR3/4/5/6/7. Some receptors are highly selective for one endogenous chemokine (monogamous receptors), whereas others are highly promiscuous and can be activated by more than one chemokine.

cohorts show significant high levels of CXCL8 mRNA or circulating protein in peripheral blood (Hu et al., 2017; Sun et al., 2021), plasma (Lu et al., 2016; Ngo et al., 2015; Prado et al., 2018), serum (Blasco et al., 2017; Ehrhart et al., 2015), cerebrospinal fluid (CSF) (Su et al., 2013; Kuhle et al., 2009; Gonzalez-Garza et al., 2018; Mennini et al., 2017; Mitchell et al., 2008; Tateishi et al., 2010) and spinal cord ventral horns (La Cognata et al., 2023). In some works, a correlation with disease and prognosis has emerged, thus proposing this humoral constituent as a systemic inflammation-related biomarker for disease severity (Sun et al., 2021; Ehrhart et al., 2015; Su et al., 2013). A concordant significant overproduction of CXCL8-mRNA and secreted protein has also been measured in ALS cultured monocyte-derived microglia-like cells (Quek et al., 2022) and in LPS-stimulated myeloid dendritic cells isolated from a subpopulation of ALS patients (Rusconi et al., 2017). Further works described an even more pronounced deregulation of the CXCR1/2 pro-inflammatory axes, reporting increased levels of CXCL1/2/8 in monocytes derived from ALS patients (Zhao et al., 2017), cultured fibroblasts and iPSC neural rosettes (Won et al., 2016), and of CXCL2/3/5/8 in peripheral blood mononuclear cells from a clustered subgroup of sporadic ALS patients (Mizwicki et al., 2012). Interestingly, recent evidence displayed the incubation of rat primary motor neurons or murine NSC-34 cells overexpressing mutant SOD1-G93A with GROα (CXCL1) and MIP2α (CXCL2) ligands reduces cellular viability and triggers apoptosis in a dose dependent manner (De Paola et al., 2007; La Cognata et al., 2023).

While the up-regulation of CXCR1/2 ligands in biological fluids, tissues and isolated cells of ALS patients, and *in vitro* preclinical models has been extensively investigated, an interesting novel implication regards the CXCR2 receptor itself. Indeed, our research group recently described a significant increase of CXCR2, at both transcriptional and protein levels, in *postmortem* primary motor cortex and lumbar spinal cord of a subgroup of sporadic ALS patients (La Cognata et al., 2021a, 2023) (Fig. 2**, panel A**) and SOD1G93A mice at symptomatic stages (Morello et al., 2017). Interestingly, we found an association trend between higher CXCR2 mRNA levels in ALS spinal cord and short survival (La Cognata et al., 2023). These findings stimulated the hypothesis of an exacerbated activation state of CXCR2 in degenerating motor neurons and the use of CXCR2 inhibition as a therapeutic strategy against ALS neurodegeneration (Fig. 2**, panel B**). We therefore prioritized and selected reparixin, a well-known CXCR2 allosteric inhibitor previously used in several human pathological conditions (metastatic triple negative breast cancer, lung transplant, pancreatic islet transplantation and severe COVID-19 pneumonia conditions) (Piersanti et al., 2023; Cambier et al., 2023), and explored the pharmacological effects mediated by reparixin in different *in vitro* and *in vivo* preclinical ALS models: i) murine NSC-34 cells overexpressing human WT or mutated (G93A) SOD1, ii) human degenerating inducible pluripotent stem cell (iPSC)-derived motor neurons, and iii) SOD1G93A mice (La Cognata et al., 2021a, 2023). In the murine NSC-34 cell-based model, cells with the G93A-SOD1 genetic background were particularly vulnerable to CXCR2 activation by CXCL1/2 ligands administration (GROα and MIP2α), while co-treatment with reparixin was able to counteract the chemokine-induced toxicity (La Cognata et al., 2023). In iPSC-derived motor neurons, reparixin showed cytological neuroprotective effects, by preventing iPSC-derived motor neurons from apoptotic cell death following growth-factors withdrawal, preserving neuronal morphology, mitochondrial membrane potential and cytoplasmic membrane integrity (La Cognata et al., 2021a). *In vivo*, reparixin was particularly effective in female SOD1G93A mice, where it delayed by four weeks the onset of neuromuscular decline and reduced body weight loss at endpoint (La Cognata et al., 2021a). This latter outcome, in particular, represents a remarkable effect when compared to riluzole and edaravone (Jaiswal, 2018). In SOD1G93A mice, riluzole treatment improves mice lifespan (Gurney et al., 1996) but has no effect on motor functions (Raoul et al., 2013; Hogg et al., 2017), while edaravone treatment slows motor decline and body weight loss by 4–11 days in female mice but does not significantly increase survival (Ito et al., 2008).

The gender-specific effects observed in our study may reflect differences in vulnerability and disease progression between males and females SOD1G93A mice. Indeed, the existence of sex-linked variable mechanisms are not novel in ALS (McCombe and Henderson, 2010; Trojsi et al., 2020; Veldink et al., 2003; Tang et al., 2019; Heiman-Patterson et al., 2005; Pfohl et al., 2015) and, in our study, reparixin treatment started in both sexes at 14 weeks of age, when females SOD1G93A mice display less evident symptoms compared to their male counterparts (La Cognata et al., 2021a). Nonetheless, this evidence arises some interesting questions about the potential impact of sex in CXCR2-CXCL1/2/8 axis signaling. Some works reported the female

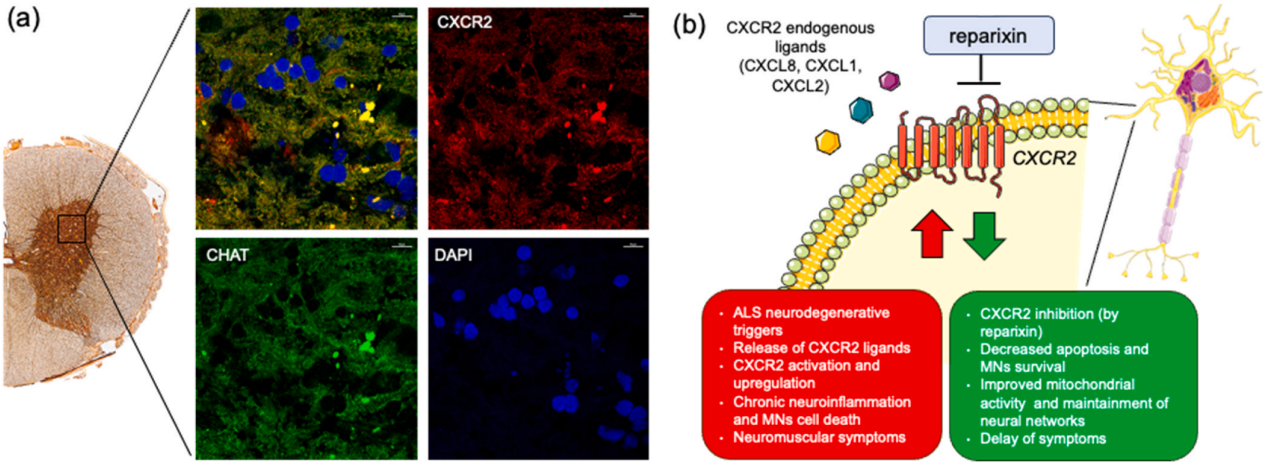

Fig. 2. CXCR2/CXCRL8 axis may contribute to ALS motor neuron degeneration. A) $CHAT^{+}$ MNs in spinal cord ventral horns showing CXCR2 immunoreactivity. Photomicrographs were obtained with a Nikon A1 confocal inverted microscope equipped with a Plan Apochromat lambda 60×/1.4 oil immersion lens (Nikon, Tokyo, Japan). Scale bar 10 μm. **B)** A scheme depicting the possible molecular mechanism involving the CXCR2/CXCL1-2–8 axis in ALS. Upon ALS degenerative triggers, CXCR2 ligands may be released in the brain microenvironment and act on MNs in an autocrine or paracrine fashion, sustaining the neuronal overexpression and activation of CXCR2. Reparixin treatment likely counteracts this inflammatory reaction, by antagonizing CXCR2, slowing down motor neuronal degeneration, enhancing motor neurons survival, maintaining neural network connections, preserving mitochondrial activity and, ultimately, alleviating neuromuscular symptoms. For further details, refer to previous studies (La Cognata et al., 2021a, 2023).

gender exhibits a milder ALS phenotype compared to male (Veldink et al., 2003; Tang et al., 2019; Heiman-Patterson et al., 2005; Pfohl et al., 2015; Frutiger et al., 2008; Watkins et al., 2020), which rather appear characterized by higher levels of CXCL8 in CSF (Mennini et al., 2017) and plasma (Ngo et al., 2015). It is plausible that the inflammatory levels mediated by this axis are lower in female SOD1G93A mice than in males. For the former, the pharmacological action elicited by reparixin could be sufficient to lower enough the exacerbated CXCR2 activation and the production of molecular mediators, alleviating the motor symptoms.

Of course, the role of CXCR1/2 and CXCL1/2/8 signaling pathways in ALS pathophysiology has not been completely elucidated and further investigations are still required to characterize the contribution of this axis in ALS and define the therapeutic relevance of CXCR2 inhibition in motor neuron selective degeneration. Nonetheless, data support CXCR2-CXCL8 axis contribution to ALS pathology and encourage future explorations.

3.2. CXCR3 - CXCL9/10/11 axis

CXCR3, also known as GPR9 or CD183, is a G protein-coupled seven-transmembrane receptor, playing a crucial role in migration of effector T cells to inflammation or tumor site, as well as in pain modulation (Aloyouny et al., 2020; Wang et al., 2022a). Depending on the composition of its amino-terminus, CXCR3 has three different isoforms: the two most studied isomers, CXCR3-A and CXCR3-B, also expressed in neuronal cells, and the less studied truncated variant, CXCR3-alt (Wang et al., 2022a; Qiao et al., 2022).

The activation of CXCR3 relies on three ELR$^-$ interferon-γ (IFN-γ)-inducible ligands: CXCL9, CXCL10 and CXCL11. Among the three, the most studied for its involvement in the pathophysiological processes of the central nervous system is CXCL10 or IFN-γ -induced protein-10 (IP-10) chemokine (Qiao et al., 2022). This latter is predominantly secreted by monocytes, T helper cells, cytotoxic T lymphocytes, dendritic cells, macrophages, endothelial cells, fibroblasts and cancer cells, and exerts major functions in immunomodulation, inflammatory cell homing, angiogenesis, axonal injury, neuropathic pain, and impaired motor function recovery (Bagheri et al., 2020).

Several works report debated data on CXCR3/CXCL10-related mechanisms in ALS. Increased CXCL10 expression levels were detected in CSF of sporadic ALS patients (Tateishi et al., 2010) and in serum of aged SOD1G93A transgenic mice (Noh et al., 2014). More recently, a higher genetically predicted circulating CXCL10 level was associated with a higher risk of ALS (Liu et al., 2023). Concordantly, ALS T cells show a significantly upregulation of CXCR3, and CXCL10 treatment produces increased migratory behavior in ALS lymphocytes (Perner et al., 2018). On the contrary, CXCL10 reduced expression levels were observed in patients with mutated *C9ORF72*, both in lymphoblastoid cells and CSF (Ismail et al., 2013).

An interesting functional association was found between neuronal CXCL10-expression and the sporadic ALS-linked gene *CREST* (Cheng et al., 2019). This latter is a calcium-regulated transcriptional activator found mutated (Q388X) in sporadic ALS patients (Cheng et al., 2019). Loss of function *CREST* mutations in mice cause deficits in motor coordination, activation of microglia, increase of proinflammatory responses and the transcriptional upregulation of CXCL10 in neurons *via* histone acetylation/deacetylation (Cheng et al., 2019).

3.3. CXCR4/7 - CXCL12 axis

CXCL12, originally named stromal cell-derived factor 1 (SDF-1), is a chemokine first cloned from a bone marrow-derived cell line and later identified as pre-B cell growth stimulating factor (PBSF). It is broadly expressed in a variety of tissue types where it acts as a potent chemoattractant for hematopoietic cells, playing an important role in homing hematopoietic stem cells to bone marrow, and mediating the survival and proliferation of progenitor cells (Sun et al., 2010; Bocchi et al., 2023). CXCL12 has six isoforms (CXCL12 α to φ) derived from alternative splicing, with CXCL12α and CXCL12β being the most widely studied subtypes (Sun et al., 2010; Bocchi et al., 2023). The α isoform is the predominant one, secreted by marrow stromal cells and endothelial cells following tissue damage, and then rapidly degraded by proteolysis in blood. The β isoform is more resistant to degradation, stimulates angiogenesis and is present in highly vascularized organs such as liver, spleen and kidney (Sun et al., 2010; Bocchi et al., 2023).

CXCL12 acts as a modulator of cell growth and survival by binding to its receptor, CXCR4, which was the first recognized chemokine receptor for human immunodeficiency virus (HIV-1) infection of CD4$^+$ lymphocytes (Cavallaro, 2013; Sun et al., 2010; Bocchi et al., 2023), and is expressed in dendritic cells, naive T cells, natural killer cells and monocytes. In mature brain, CXCL12 and CXCR4 are constitutively expressed by neurons and glial cells, and are implicated in several brain processes, such as development, cell migration, neuronal survival and neurotransmission (Cavallaro, 2013). The CXCL12/CXCR4 interaction was believed to be unique, until the cloning and identification of CXCR7 which acts as an atypical endogenous β-arrestin-coupled receptor (Cavallaro, 2013; Sun et al., 2010; Bocchi et al., 2023).

The first data regarding the implication of CXCR4/CXCL12 in ALS were obtained in cellular-based mouse models. Immortalized glial restricted precursors derived from mouse E11.5 neural tubes of SOD1G93A mutant mice showed reduced levels of CXCR4, causing impaired cellular migration (Luo et al., 2007). Moreover, transplantation of neural stem cell subpopulation double positive for the cell surface marker Lewis X and CXCR4 into SOD1G93A transgenic mouse was able to modify disease's progression, by delaying the onset and significantly increasing survival (Corti et al., 2007). In mouse Thy1 motor-neurons (characterized by ALS syndromes with hypoactivity followed by hindlimb paralysis, respiratory distress, and, ultimately, death), CXCR4 and its antagonizing ligand CXCL12 undergo early autocrine and proteostatic deregulation, intracellular sequestration and aggregation as a result of Ranbp2 loss (Cho et al., 2017).

More recently, immunohistochemistry and biochemical research focusing on CXCR4/7-CXCL12 axis has been conducted in control and ALS patients. Andrés-Benito et al. described CXCR4 expression in a subset of oligodendroglial-like cells and axonal ballooning of motor neurons in sALS patients; CXCR7 in motor neurons of control and sALS, as well as in reactive astrocytes in the ALS-patients' pyramidal tracts, while CXCL12 immunoreactivity was localized in motor neurons of both control and sALS and in a few glial cells at the terminal stage (Andres-Benito et al., 2020). Furthermore, significantly higher CXCL12 levels were detected in CSF of sALS patients, thus identifying this chemokine as a complementary biomarker for sALS diagnosis (Andres-Benito et al., 2020). Accordingly, T cells from sALS patients showed CXCR4 upregulation compared to age-matched healthy controls (Perner et al., 2018).

Experimental evidence about the usefulness of therapeutic modulation of CXCR4/7-CXCL12 axis in derive from the study by Rabinovich-Nikitin et al (Rabinovich-Nikitin et al., 2016). Chronic administration of AMD3100, a CXCR4 antagonist, to SOD1G93A mice improves microglial pathology, decreases pro-inflammatory cytokines and blood-spinal cord barrier permeability, and increases motor neurons count in the lamina X area of the spinal cord, finally resulting in a significant extension of mouse lifespan, as well as preserved motor function and weight loss (Rabinovich-Nikitin et al., 2016). Therefore, this axis probably plays a complex role in inflammation, oligodendroglial-astrocytic signaling and neuronal preservation in ALS, and approaches aimed at targeting CXCR4 might have interesting clinical implications.

3.4. CXCR5 - CXCL13 axis

CXCL13, also known as B lymphocyte chemoattractant (BLC) or B cell attracting chemokine 1 (BCA-1), is primarily involved in the

recruitment of B cells and exert a migratory effect on a small number of T cells and macrophages T cells (Pan et al., 2022; Harrer et al., 2022; Wang et al., 2022b). It is mainly expressed by stromal cells, including follicular dendritic cells and macrophages, and plays a key function in coordinating cell migration within different regions of the secondary lymphoid organ (spleen, lymph nodes and Peyer's patches) especially under pathological conditions (Pan et al., 2022; Harrer et al., 2022; Wang et al., 2022b).

CXCL13 exerts its action *via* the cognate receptor CXCR5 (also called BLR1), which mediates biological functions through specific downstream interactions. In lymph nodes, the CXCR5/CXCL13 axis is essential for homing $CXCR5^{+}$ B lymphocytes to lymphoid tissue, and CXCR5-deficient mice present serious immune system defects (Pan et al., 2022; Harrer et al., 2022; Wang et al., 2022b). Due to its ~40% amino acid homology with CXCR1, CXCR5 shares with CXCR1 a similar activation pathway, including spurring intracellular Ca^{2+} inward flow and ERK/-MAPK signaling mediated by the second intracellular domain of CXCR5 (Pan et al., 2022; Harrer et al., 2022; Wang et al., 2022b). However, its precise action mechanisms remain unclear.

Recently, a possible involvement of CXCR5/CXCL13 axis in ALS has been proposed by virtue of *in vitro* and *in vivo* experimental paradigms on transgenic SOD1 ALS mouse models and tissue samples from human ALS subjects (Trolese et al., 2020). A selective overexpression of both CXCR5 and CXCL13 was found in laser captured motor neurons of mutant SOD1 fast progressing mice (Trolese et al., 2020). The release of CXCL13 in the CSF of ALS mice progressively increased with aging, suggesting that CXCL13 might act at distant sites throughout disease progression (Trolese et al., 2020). Intra-cerebroventricular neutralization of CXCL13 in ALS mice results in exacerbation of motor functional impairment and decreased survival. Accordingly, CXCL13 knock-down in primary spinal motor neuron/glial co-cultures showed exacerbated motor neuron death, while addition of CXCL13 prevented it (Trolese et al., 2020). Along with data collected in mice, both ligand and receptor are upregulated in motor neurons of ALS patients, while CXCL13 levels were lower in patients' CSF (Trolese et al., 2020). Altogether these data suggest the involvement of CXCR5/CXCL13 axis in ALS pathophysiology, supporting the hypothesis that motor neuronal cells activate CXCL13 signaling to attenuate neuroinflammation and prevent neuromuscular denervation. These findings indicate CXCL13 may be a potential clinical adjunct to discriminate ALS from other neurological diseases and stimulation of its axis may be useful for therapeutic approaches (Trolese et al., 2020).

4. In ALS pathophysiology, CXCL/CXCR axes exhibit distinct dynamics in the nervous system and periphery

Altogether, the above listed studies involving CXCRs/CXCLs in ALS show no common pattern of expression, activation or mediated biochemical events. Instead, there is great functional variability and, once activated, CXC axes may translate the external signals into a multiplicity of downstream intracellular pathways (e.g., c-Raf/MAPK/AP-1, p-PKC-μ/p-ILK/NLRP3, JAK2/STAT3, TAK1/NF- κ), which in turn may mediate a vast number of biological functions, including cellular motility state, cell migration and neuronal damage (Jiang et al., 2023). If on one side the aspect of *redundancy* (wherein most receptors can be activated by multiple chemokine ligands and most chemokines can activate multiple receptors) of this superfamily has been demonstrated (Eiger et al., 2021), on the other side it is now appreciated that many chemokine/receptor interactions display *biased agonism*, a phenomenon in which different ligands binding to the same receptor signal through different pathways with different efficacies, leading to distinct biological effects (Eiger et al., 2021). Changes in ligands (e.g., the type of ligand, the concentration, the oligomeric state), receptors (e.g., the encoded protein isoform, the conformational modifications, the internalization mechanisms, the phosphorylation sites), or specific cytological or histological context (*system*) may result in distinct signaling axis modulation and biological responses (Eiger et al., 2021; Nasser et al., 2007). These type of dynamics are starting to emerge also for other families, such as the TGF-β family ligands and receptors (Miller et al., 2019).

Remarkably, many of CXC receptors (in the first place, CXCR2), as well as their endogenous ligands, are synthetized by both peripheral immune cells (neutrophiles, T and B lymphocytes, NK cells) and non-immune cells of the nervous system (microglia, astrocytes, cells from oligodendrocyte lineage and specialized neurons) (McKimmie and Michlmayr, 2014), and their expression dynamically change during ALS progression. In addition, distinct biological actions exerted by these chemokine/receptor interactions have been described in central and peripheral nervous system, which are both involved in ALS pathogenesis (Jiang et al., 2023; Gentile et al., 2019). Indeed, while in the central nervous system chemokine/receptor axes are enrolled in controlling homeostasis, synaptic transmission and neuroinflammatory responses, in the peripheral nervous system they are involved in pain/nociception signaling regulation (Jiang et al., 2023; Silva et al., 2017).

5. Conclusion

A plethora of evidence from numerous studies utilizing several experimental approaches (biochemical analysis, small molecule receptor antagonists/agonists, neutralizing antibodies of CXC chemokine receptors, animal models deficient in or overexpressing CXC receptors and/or their ligands) support the implication of four main CXC chemokines/cognate receptors signaling axes (CXCR1/2-CXCL1/2/8; CXCR3-CXCL9/10/11; CXCR4/7-CXCL12; CXCR5-CXCL13) in the pathophysiology of ALS (Fig. 3). These chemokines have important roles in inflammation or immune surveillance, and may significantly contribute to ALS pathology. Despite a large number of clinical trials based on anti-inflammatory agents found no protection so far, it is emerging that ALS is a phenotypically and genetically heterogenous disease, so effective treatments may necessitate stratified case monitoring (La Cognata et al., 2021b). The specific pharmacological manipulation of CXC chemokines and receptors could have a strategic therapeutic value in the context of ALS subgroups, or be useful as an adjuvant therapy. Moreover, CXC-based immunological biomarkers may be useful for precise tracking of immune responses, from preclinical to the end disease stages, thus guiding precision medicine. A better understanding of CXCLs/CXCRs biology may allow for the effective utilization of these immune and inflammatory mediators in ALS therapy.

Ethics approval and consent to participate

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CRediT authorship contribution statement

Cavallaro Sebastiano: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Guarnaccia Maria:** Funding acquisition, Writing – review & editing. **Morello Giovanna:** Writing – review & editing. **La Cognata Valentina:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

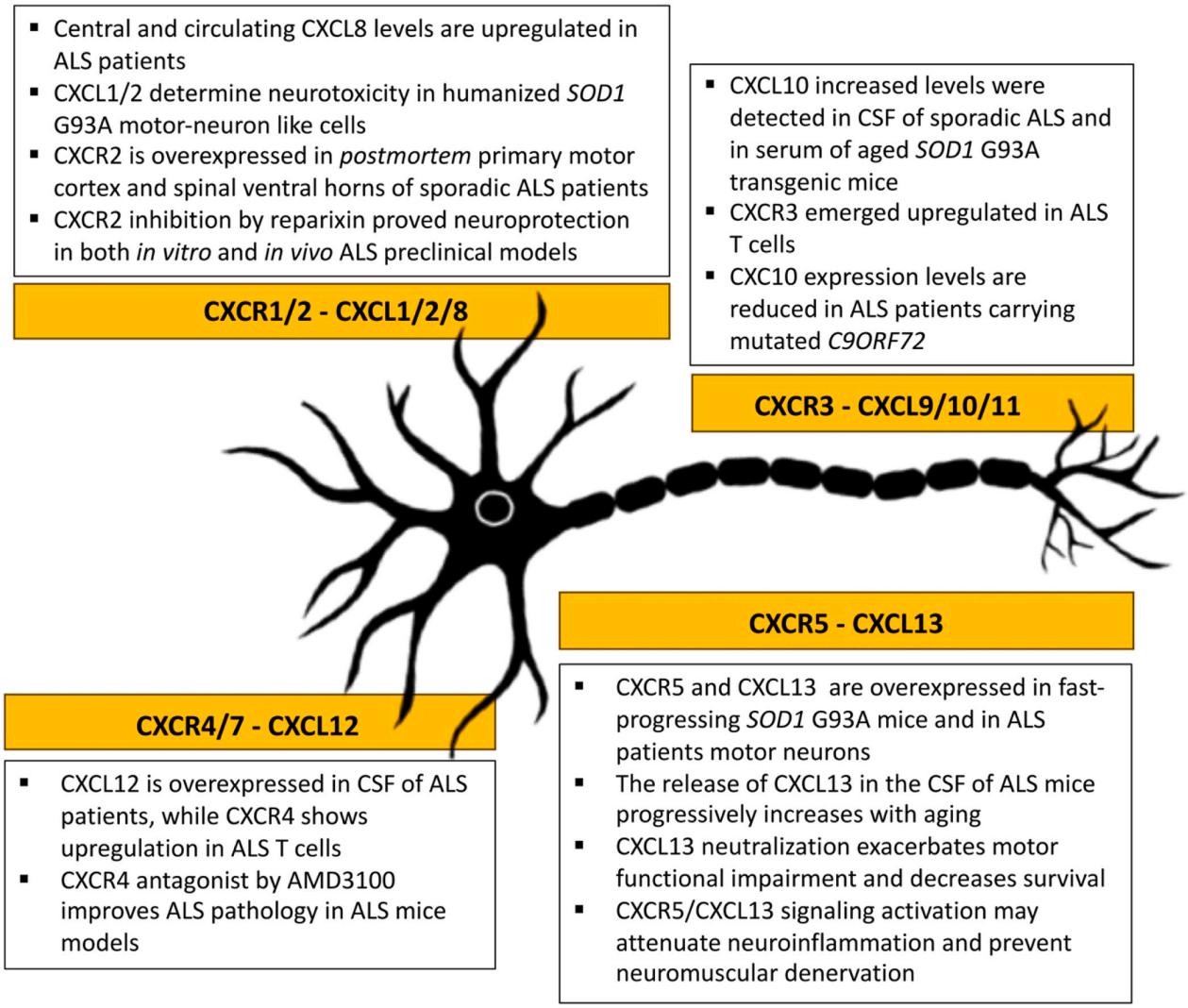

Fig. 3. Schematic diagram summarizing the four main CXC chemokines/cognate receptors axes involved in the pathophysiology of ALS. A plethora of evidence from numerous studies reviewed in the present work support the implication of four CXC chemokines/cognate receptors axes in ALS pathology. Main findings for each axis are stated in the figure.

the work reported in this paper.

Data availability

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

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Competing interests

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2024.102587.

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