frontiers | Frontiers in Aging Neuroscience

REVIEW
published: 03 May 2022
doi: 10.3389/fnagi.2022.890958

Neuroimmune Crosstalk Between the Peripheral and the Central Immune System in Amyotrophic Lateral Sclerosis

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Specialty section:
This article was submitted to Neuroinflammation and Neuropathy, a section of the journal Frontiers in Aging Neuroscience

Received: *07 March 2022*
Accepted: *14 April 2022*
Published: *03 May 2022*

Citation:
Yu W, He J, Cai X, Yu Z, Zou Z and Fan D (2022) Neuroimmune Crosstalk Between the Peripheral and the Central Immune System in Amyotrophic Lateral Sclerosis. Front. Aging Neurosci. 14:890958. doi: 10.3389/fnagi.2022.890958

Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by the degeneration and death of motor neurons. Systemic neuroinflammation contributes to the pathogenesis of ALS. The proinflammatory milieu depends on the continuous crosstalk between the peripheral immune system (PIS) and central immune system (CIS). Central nervous system (CNS) resident immune cells interact with the peripheral immune cells *via* immune substances. Dysfunctional CNS barriers, including the blood–brain barrier, and blood–spinal cord barrier, accelerate the inflammatory process, leading to a systemic self-destructive cycle. This review focuses on the crosstalk between PIS and CIS in ALS. Firstly, we briefly introduce the cellular compartments of CIS and PIS, respectively, and update some new understanding of changes specifically occurring in ALS. Then, we will review previous studies on the alterations of the CNS barriers, and discuss their crucial role in the crosstalk in ALS. Finally, we will review the moveable compartments of the crosstalk, including cytokines, chemokines, and peripheral immune cells which were found to infiltrate the CNS, highlighting the interaction between PIS and CIS. This review aims to provide new insights into pathogenic mechanisms and innovative therapeutic approaches for ALS.

Keywords: amyotrophic lateral sclerosis, crosstalk, peripheral immunity, CNS barriers, CNS immunity

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease typically characterized by adult-onset dysfunction of both upper and lower motor neurons (MNs). The incidence rates of this fatal disease were 1.38 (urban China), 1.5 (United States), 2.08 (Europe) per 100,000 persons (Xu et al., 2020; Burchardt et al., 2022; Mehta et al., 2022), and most patients died within 3–5 years after disease onset (Chia et al., 2018). No clinical therapies have been proven effective except for riluzole

and edaravone, which can only delay disease progression (Chen et al., 2016; Scott, 2017; Shefner et al., 2020). The mechanisms underlying ALS pathogenesis are not yet fully understood. ALS is a multifaceted disease, and several mechanisms, including pathogenic gene mutations (Cervantes-Aragón et al., 2020), neuroinflammation (Beers and Appel, 2019), autophagy, mitophagy (French et al., 2018), necrosis (Yuan et al., 2019), aggregation of toxic proteins (Wei et al., 2017), dysfunction of energy metabolism (Vandoorne et al., 2018), and environmental factors (French et al., 2018), have been proven to participate in its pathogenesis.

Accumulating evidence indicates abnormalities in the immune system throughout ALS (Dutta et al., 2020; Theoharides and Tsilioni, 2020). Immune cells are activated and lead to a chronic proinflammatory microenvironment in both the peripheral and central nervous systems in ALS (Masrori et al., 2022). The pro-inflammation in ALS is systemic, and crosstalk exists between the peripheral immune system (PIS) and the central immune system (CIS). To date, crosstalk has not been well defined. With the development of insights into the understanding of ALS, researchers have realized the importance of the continuous interaction and communication of these two systems. CNS resident immune cells and peripheral immune cells interact with each other *via* immune molecules. Dysfunctional CNS barriers, including the blood–brain barrier (BBB) and the blood–spinal cord barrier (BSCB), open the gate for "crosstalk" and are also regulated by the inflammatory environment. As a result, chronic systemic inflammation contributes to the death of MNs, injuring motor neuron axons, and the dysfunction of neuromuscular junctions (Sweeney et al., 2019; Wu Y. et al., 2020; Pan and Nicolazzo, 2022; **Figure 1**).

MAJOR CHANGES OF RESIDENT IMMUNE CELLS IN AMYOTROPHIC LATERAL SCLEROSIS

Inflammation in Central Nervous System in Amyotrophic Lateral Sclerosis

Inflammation is widespread in the CNS in ALS (Beers and Appel, 2019; Liu et al., 2021). Glial cells, including microglia and astrocytes, trigger neuroinflammatory reactions, interact with infiltrated peripheral immune cells and eventually induce or accelerate neuronal death in CNS in ALS (Cragnolini et al., 2020). Microglia are the resident innate immune cells of the CNS, and mediate the neuroinflammation *via* the release of immune molecules including cytokines and chemokines. Microglia activation is heterogeneous and dependent on the nature of the pathological insult (Mattei and Notter, 2020). Researchers have categorized activated microglia into two opposite types: M1 (toxic or proinflammatory) or M2 (neuroprotective or anti-proinflammatory) microglia (Guo et al., 2022). However, researchers have recently realized that there is a continuum of phenotypes between M1 and M2 in ALS (Li et al., 2019), such as disease-associated microglia (DAM) (Krasemann et al., 2017; Dols-Icardo et al., 2020) and receptor-interacting protein kinase 1 (RIPK1)—regulated inflammatory microglia (RRIMs) (Mifflin et al., 2021). In general, accumulating studies have proven that microglia show an anti-inflammatory phenotype and protect MNs at the onset of the disease, while end-stage microglia shift to a proinflammatory phenotype and aggravate the neurodegeneration of MNs in ALS (Liu et al., 2021; Masrori et al., 2022). Astrocytes are the most common glial cells in the brain, maintain the CNS barriers (Signorile et al., 2021), secrete neurotrophic and neuroprotective factors, regulate neurotransmitter uptake and recycling, and promote neurogenesis (Gharbi et al., 2020). Studies have identified a role for astrocytes as immune modulators, as they may control the activation, migration, and proliferation of microglia (Sunnemark et al., 2005; Ouali et al., 2018).

Immune Activation in the Periphery in Amyotrophic Lateral Sclerosis

Peripheral immune abnormalities exist in ALS (McCombe et al., 2020). In general, the chronic peripheral immune response is proinflammatory in ALS. Lymphocytes, monocytes (including macrophages), neutrophils, natural killer (NK) cells, and mast cells (MCs) are peripheral resident immune cells. ALS patients were found to have elevated total leukocyte counts in blood (Murdock et al., 2017). In peripheral blood, most studies suggest decreased levels of neuroprotective CD4 T lymphocytes while the subgroup of CD4 T lymphocytes, regulatory T cells (Tregs), are reduced and dysfunctional in ALS patients. In ALS, the number of cytotoxic CD8 T lymphocytes in peripheral blood is controversial. NK T lymphocytes are thought to be harmful in ALS and are increased in peripheral blood in patients with ALS (Finkelstein et al., 2011; Perner et al., 2018; Giovannelli et al., 2020; Nishihara et al., 2020; Rolfes et al., 2021). B lymphocytes are merely discussed in ALS and studies suggest that they play a supplementary role in the pathogenesis of ALS (Naor et al., 2009; Pennati et al., 2018). Alterations in the proportion of monocytes were reported and circulating monocytes from ALS patients preferentially differentiated to a proinflammatory phenotype (Liu et al., 2016; Du et al., 2020). The numbers of neutrophils are increased in the peripheral blood and show a significant correlation with disease progression (Murdock et al., 2017; Leone et al., 2022). NK cells are innate immune cells and mediate cytotoxicity. Levels of NK cells in the blood of ALS patients are increased and could be pathogenic (Gustafson et al., 2017; Murdock et al., 2017). An increased number of circulating MCs was shown in ALS mice while there was a lack of evidence in ALS patients (Trias et al., 2018; Harcha et al., 2021).

Distal axonopathy is a recognized pathological feature of ALS (Nardo et al., 2016). Recruitment of activated MCs, macrophages, and neutrophils along the degenerating motor axons in sciatic nerves and skeletal muscle is observed in ALS (Chiu et al., 2009; Angelini et al., 2020; Trias et al., 2020). Peripheral immune cells can also infiltrate into CNS and exert an effect on motor neurons and glial cells, which will be discussed below. Peripheral immune cells have been increasingly discussed in their prognostic role. In this regard, with the development of technology and

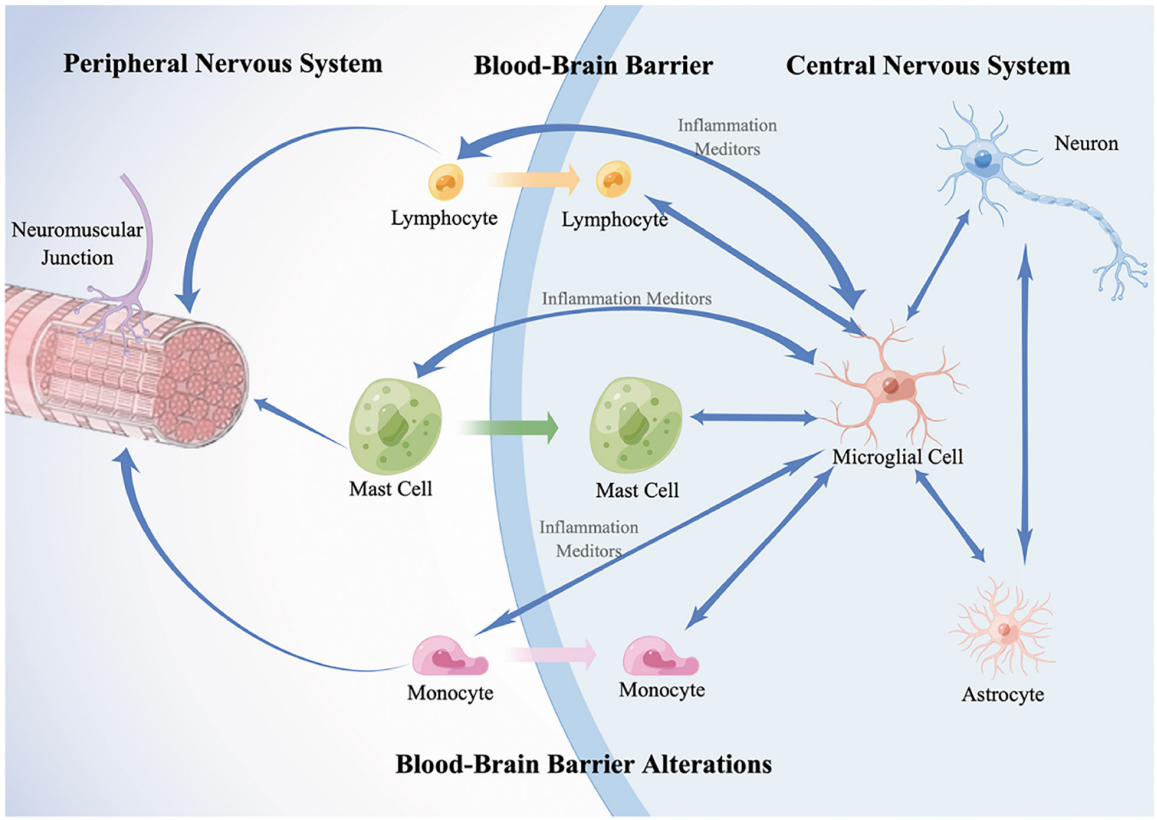

FIGURE 1 | A schematic diagram of immune crosstalk between PNS and CNS. In the CNS, resident immune cells, microglia, are activated and mediate the neuroinflammation by the release of proinflammatory or anti-inflammatory substances such as cytokines and interact with infiltrated peripheral immune cells; astrocytes control the activation, migration, proliferation of microglia. In the PNS, resident immune cells, including T lymphocytes, mast cells, and monocytes are activated and infiltrate along the peripheral motor nerve and neuromuscular junction. Meanwhile, they infiltrate into CNS triggered by microglia-derived inflammation mediators. In addition, dysfunction of CNS barriers, including the blood-brain barrier (BBB) and the blood-spinal cord barrier (BSCB), contribute to the infiltration of peripheral immune cells and accelerate the harmful interaction. As a result, inflammatory responses spread across the two systems contribute to the death of motor neurons (MNs), injuring MN axons, and the dysfunction of neuromuscular junctions. Double-headed arrows represent the communication of two cells. Blue single arrows represent that the cells release inflammatory mediators and influence their targets. Orange, green, and purple arrows represent that the peripheral cells infiltrate into the CNS, respectively.

understanding, researchers have turned to exploring a specific population or a single myeloid subpopulation to categorize or monitor patients (Murdock et al., 2017; Leone et al., 2022).

ALTERATION OF THE CENTRAL NERVOUS SYSTEM BARRIERS IN AMYOTROPHIC LATERAL SCLEROSIS

CNS barriers are formed by a layer of endothelial cells, connected by inter endothelial tight junctions (TJs), adhesion proteins, and cytoplasm (Bull et al., 2022). A basement membrane called the basal lamina (BL) ensheathed by pericytes and astrocytic end-feet supports endothelial cells and associated pericytes (Lochhead et al., 2020; Yu et al., 2020). They make up the physical barriers of the CNS while the biochemical barriers of CNS are imparted by various transport systems. Alterations in brain barriers have been observed in the early stage in ALS patients and mice, suggesting that the impairment may contribute to the pathogenesis (Bull et al., 2022). The alterations are summarized as follows: disruption of the integrity of physical barriers, function modulation of biochemical barriers, and secretion of neuroimmune-related substances by barrier cells in the immune response (Erickson and Banks, 2018; Kakaroubas et al., 2019; Gil-Martins et al., 2020). CNS barriers act as the center point in humoral-based communications between the CIS and PIS. A better understanding of how the integrity or function of CNS barriers is altered may provide approaches to terminate the harmful crosstalk in ALS.

Disruption of the Integrity of Physical Barriers in Amyotrophic Lateral Sclerosis

Multiple studies have found alterations of the ultrastructure of CNS barriers in ALS patients, including swelling and cytoplasmic vacuolization of microvascular endothelial cells, reduced pericyte coverage, and detachment of astrocyte end-feet processes from endothelial cells in the spinal cord of ALS patients (Miyazaki et al., 2011; Garbuzova-Davis et al., 2012; Yamadera et al., 2015).

Ultrastructural alterations have also been observed in the brain stem and cervical and lumbar spinal cords, but not in the motor cortex of ALS mice. The alterations have been noted to occur at the early disease stage and worsen with disease progression (Garbuzova-Davis et al., 2012; Winkler et al., 2013). TJs are formed by multiple proteins, such as zonula occludens-1 (ZO-1) and occludin, and prevent the paracellular movement of solutes (Winkler et al., 2013). A significant reduction in the expression of TJs and adhesion proteins such as ZO-1 and occludin was observed in the spinal cord of both ALS patients and mice (Pan and Nicolazzo, 2022). Despite the change in adhesion proteins, the morphological structures of TJs were found to be well preserved under electron microscopy in the spinal cord of postmortem ALS patients (Sasaki, 2015). Although morphological structures of TJs are preserved, the detection of endogenous proteins in the CNS suggests the increased paracellular permeability and leakiness of CNS barriers (Waters et al., 2021). Furthermore, BL thickening is observed in both ALS patients and mice. The detachment of endothelial cells exposes BL to plasma proteins, fibrin, and collagen IV within the BL, which then accumulate, leading to BL thickening (Sasaki, 2015). As BL abnormalities are detected in the early stage of ALS mice, these findings suggest that it may occur as a compensatory mechanism or a reparative process (Nguyen et al., 2021). Based on these findings, ultrastructural abnormalities and reduced expression of TJs adhesion proteins may contribute to compromised junctional integrity and an increase in paracellular permeability, permitting peripheral substances and cell access to the CNS. Therefore, it improves the communication of PIS and CIS, and accelerates the systemic proinflammation.

Functional Modulation of the Biochemical Central Nervous System Barriers

Biochemical CNS barriers are imparted by various transport systems, such as ATP-binding cassette (ABC) protein. They can effectively exclude various endogenous and exogenous toxins from the endothelial cells to maintain cellular homeostasis. The most well-studied ABC protein, P-glycoprotein (P-gp), is a major efflux transporter for small, lipid-soluble molecules expressed on CNS barriers (Gil-Martins et al., 2020). The expression and activity of P-gp are upregulated in both ALS patients and mice (Jablonski et al., 2012; Qosa et al., 2016; Chan et al., 2017; van Vliet et al., 2020). Tumor necrosis factor α (TNF-α) and growth factor-beta 1(TGF-β1) were shown to upregulate the expression and activity of P-gp in mice and rats (Dohgu et al., 2004; Bauer et al., 2007). As levels of TNF-α and TGF-β1 are increased in ALS patients and mice (Bougea, 2019; Tortelli et al., 2020), they are associated with the overexpression of P-gp. Moreover, astrocytes are also suspected to be responsible for the increased expression of P-gp in ALS dependent on ALS genotypes. For example, cocultured ALS-associated-mutant SOD1 astrocytes impacted P-gp in nearby endothelial cells by secreting soluble factors such as TNF-α, chemokines, and reactive oxygen species (ROS) (Ji et al., 2013). Meanwhile, ALS-associated mutant C9orf72 astrocytes have been shown to have no effects on endothelial P-gp expression (Mohamed et al., 2019). Additionally, the expression of breast cancer resistance protein (BRCP), another efflux transporter, is upregulated in ALS patients and mice (Jablonski et al., 2012; Chan et al., 2017; van Vliet et al., 2020). In general, the increased P-gp and BRCP abundance and activities at the CNS barriers suggest the modulation of interface functions of biochemical CNS barriers, which may ultimately influence the development of ALS.

Barrier Cells Secrete Neuroimmune-Related Substances in the Immune Response

Barrier cells, including endothelial cells, pericytes, and astrocytes, secrete neuroimmune-related substances in response to immune stimulation from peripheral or central immune cells. Brain endothelial cells (BECs) can constitutively secrete interleukin 6 (IL-6), prostaglandins, and nitric oxide in response to different stimuli (Iannucci et al., 2020; Charoensaensuk et al., 2021). As the number of pericytes is reduced in ALS (Winkler et al., 2013), its inflammatory-mediated role may also contribute to ALS pathologies. Compared to other barrier cells, pericytes are the most sensitive to TNF-α and can release IL-6 and macrophage inflammatory protein-1α (MIP-1α, also known as CCL3) in response (Matsumoto et al., 2014). Inflammatory reactive pericytes support neutrophil transmigration by the release of IL-8 and matrix metalloproteinase-9 (MMP-9), leading to the subsequent development of neuroinflammation (Pieper et al., 2013). Astrocytes are activated in the immune response in ALS. On the one hand, astrocytes control the activation, migration, and proliferation of microglia *via* multiple inflammatory factors, and secrete proteins such as MCP-1 which mediates monocyte migration to amplify neuroinflammation in the CNS (Ouali et al., 2018; Izrael et al., 2020). On the other hand, biochemical substances such as nitric oxide, vascular endothelial growth factors (VEGF), glial cell line-derived neurotrophic factor (GDNF), and MM-9 released from reactive astrocytes on barriers regulate the expression of TJ proteins and the proliferation of endothelial cells, thus influencing the integrity and permeability of CNS barriers (Spiller et al., 2019; Izrael et al., 2020; Takata et al., 2021; Qin et al., 2022). Therefore, barrier cells can not only transfer information from one side to the other side (such as PIS to CIS) but are also involved in mediating the inflammatory microenvironment.

THE CROSSTALK FROM THE PERIPHERAL IMMUNE SYSTEM TO THE CENTRAL NERVOUS SYSTEM CONTRIBUTES TO THE SYSTEMIC INFLAMMATORY MILIEU OF AMYOTROPHIC LATERAL SCLEROSIS

In ALS, injured MNs interact with glia, and they release certain levels of cytokines and chemokines, followed by the recruitment of innate and adaptive immune cells to infiltrate the CNS to promote inflammation. Proinflammatory signaling spreads from

CIS to PIS and from PIS to CIS, thereby contributing to the systemic inflammatory milieu of ALS.

Cytokines and Chemokines in Amyotrophic Lateral Sclerosis

Many cytokines and chemokines, such as IL-1, IL-6, TNF, and CC chemokine ligand 2 (CCL2), have been shown to cross CNS barriers while the barriers mediate their transport, penetration, and uptake (Zhao et al., 2020; Bull et al., 2022). On the one hand, due to the activation of immune cells, the levels of cytokines and chemokines are significantly changed in ALS (Sun et al., 2022). Their major roles in PIS or CIS in ALS are summarized in **Table 1**. On the other hand, elevated levels of proinflammatory mediators increase the permeability of the CNS barriers, act directly on their receptors to alter the function of resident cells, induce immune cell trafficking, and exacerbate barrier disruption and neuroinflammation (Wang et al., 2014; Banks, 2015; Erickson et al., 2020).

Central Nervous System Infiltration of Peripheral Immune Cells in Amyotrophic Lateral Sclerosis

Increasing evidence shows that many peripheral leukocytes are first activated in PIS and then migrate into the CNS in ALS

TABLE 1 | The major role of cytokines and chemokines in ALS.

Molecules	Secreting cells	Change in ALS	Role in the immune system	References
TNF-α	Macrophages, T lymphocytes, NK cells	Increased	Proinflammation: activation of immune cells	Tortarolo et al., 2017; Bougea, 2019
IL-1β	Monocytes, macrophages; M1 microglia	Increased	Proinflammation: activation of immune cells	Italiani et al., 2014; Sun et al., 2022
IL-6	Immune cells, endothelial cells, myocytes	Increased/unchanged	Proinflammation: activation of immune cells	Martinez-Merino et al., 2018; Pronto-Laborinho et al., 2019; Wosiski-Kuhn et al., 2019
IL-8/CXCL8	Monocytes, endothelial cells	Increased	Proinflammation: recruitment of neutrophils, activation of glial cells	Rusconi et al., 2017
IL-10	Monocytes, T lymphocytes, and B lymphocytes; immunosuppressive microglia (M2)	Increased/increased in the early stage and decreased during disease progression	Anti-inflammation: limiting excessive production of proinflammatory cytokines, ROS.	Batista et al., 2009; Noh et al., 2014; Strickland et al., 2020
IL-13	Th2 cells, CD4 cells, natural killer T cells, mast cells, basophils, eosinophils, and neurocytes	Increased	Controversial mechanism: proinflammation: enhancing MCP-1 expression in monocytes and macrophages; anti-inflammation: induce infiltration to the injured spinal cord and anti-inflammatory polarity of macrophages	Shi et al., 2007; Lu et al., 2016; Amo-Aparicio et al., 2021
IL-17a	Th17 cells, $CD8^+$ T cells, mast cells; astrocytes	Increased	Proinflammation	Fiala et al., 2010; Jin et al., 2021
IL-33	Multiple cells	Induced	Anti-inflammation: decreasing the proportion of $CD4^+$ and $CD8^+$ T cell populations, regulating mast cells function	Lin et al., 2012; Korhonen et al., 2019
G-CSF	Monocytes and macrophages	Induced	Dual mechanism: inducing mobilization of bone marrow cells from bone to the peripheral, stimulating proliferation, inducing the recruitment of microglia in the damaged areas	Salamone et al., 2020
CXCL13	MNs	Increased	Anti-inflammation	Trolese et al., 2020
CXCL12	Bone marrow stromal cells	Increased	Proinflammation: development of T and B lymphocytes, influencing survival of mature Lymphocytes, microglial pathology, and permeability of CNS barriers	Li and Ransohoff, 2008; Rabinovich-Nikitin et al., 2016
CX3CL1	MNs, microglia	Increased	Proinflammation: activation of microglia	Zhang et al., 2018
CCL2	MNs, microglia, astrocytes	Increased	Proinflammation: activation and recruitment of NK cells, T cells	Garofalo et al., 2020
CCL5	T lymphocytes,macrophages, endothelial cells	Increased	Proinflammation: proliferation and activation of T lymphocytes, monocytes	Perner et al., 2018
CCL18/MIP-4	DC	No changed	Proinflammation: attracting lymphocytes toward DC and activated macrophages, activation of microglia	Martinez-Merino et al., 2018

TNF-α, Tumor Necrosis Factor; IL, Interleukin; G-CSF, Recombinant Human Granulocyte-Colony Stimulating Factor; CCL, C-C Motif Ligand; CX3CL1, C-X3-C Motif Chemokine Ligand 1; CXCL, C-X-C Motif Chemokine Ligand; MIP-4, Macrophage Inflammatory Protein-4; DC, Dendritic Cell.

(Angelini et al., 2020). The regulation of leukocyte trafficking to the CNS is multifaceted and depends on the activation state of the leukocytes, TJ complexes at the endothelial interface, and the inflammatory microenvironment in the CNS and PNS (Congdon et al., 2019; Trolese et al., 2020; Marchetti et al., 2022). As peripheral leukocytes can be easily monitored, and intrathecal or intracerebroventricular is associated with several risks, targeting peripheral leukocytes may be feasible in ALS treatment. Therefore, a better understanding of how peripheral immune cells infiltrate into the CNS is needed.

T Lymphocytes

The infiltration of T lymphocytes in ALS is well-known (Rolfes et al., 2021). Chemokines and chemokine receptors are critical for parenchymal infiltration. The chronic inflammatory milieu induces the upregulation of leukocyte cell adhesion on the surface of endothelial cells, which binds to CD6 expressed on T lymphocytes, allowing their entry into the brain parenchyma (Larochelle et al., 2012). In addition, T lymphocyte-derived TNF-α and IL-17 induce the secretion of MM-9 in immune cells and MNs, facilitating T lymphocyte infiltration into the CNS (Song et al., 2015). A large amount of evidence highlights the differences between T-cell subsets and their specific mechanisms of entry into the CNS in ALS. For example, endothelial cells secrete chemokines such as CXCL9, CXCL10, CXCL11, CCL19, CCL21, and MCP-1 to recruit $CD4^+$ T cells through CNS barriers. Treg cells, which have an inhibitory effect on neuroinflammation, are activated and recruited to the CNS *via* CCL5/CCR5 and CCL6/CCR6 mechanisms to inhibit the activation of microglia in the early phase of the disease (Zhao et al., 2012; Beers et al., 2017). $CD8^+$ T cells show intense infiltration and induce MN death *via* MHC-I expressed in activated microglia and injured MNs (Coque et al., 2019; Liu et al., 2020).

Mast Cells

Findings in previous studies suggested that MCs play a role in early degeneration in the PNS and have a ripple effect on neuronal damage (Trias et al., 2018; Angelini et al., 2020). Later studies confirmed the infiltration of MCs in the spinal cord of ALS patients (Fiala et al., 2010; Kovacs et al., 2021). The expression of receptors on MCs is affected by IL-6, CCL5, and TNF-α released by activated microglia, resulting in the regulation of MC activation and CNS recruitment (Jones et al., 2019). Moreover, MCs can release proteases to TJs and extracellular matrix components, thus influencing the permeability and integrity of the BBB and leading to CNS invasion of MCs (Mattila et al., 2011; Jones et al., 2019).

Monocytes

Limited numbers of activated peripheral monocytes infiltrate the CNS and influence neuroinflammation in ALS (Chiot et al., 2020). Previous studies indicate an alteration in the proportion of monocytes in ALS (Mcgill et al., 2021). In patients with rapidly progressing ALS, monocytes in the peripheral circulation are usually in a proinflammatory state (Zhao et al., 2017). Recently, peripheral monocytes have been proven to infiltrate the CNS, which is related to improved motoneuron survival in ALS, but infiltration may be limited (Peake et al., 2017). In addition, monocyte-derived macrophages are activated in ALS. Activated macrophages exert neuroprotective functions by misfolding protein clearance during the disease (Chiu et al., 2009; Shiraishi et al., 2021). Macrophages also showed limited infiltration to the CNS. The evidence may suggest that the accumulating monocytes in the CNS were due to the proliferation of infiltrated cells instead of the infiltration of accumulated circulated monocytes (Chiot et al., 2020).

Other Immune Cells: Neutrophils, Natural Killer Cells

Few studies have discussed the role of neutrophils and NK cells in neuroimmune crosstalk. However, considering that there is a significant correlation between an increase in the number of neutrophils and NK cells in the peripheral blood and disease progression (Murdock et al., 2017; Leone et al., 2022), and their role in innate immune responses, it is believed to affect neuroinflammation of the CNS in complicated ways. For example, end-stage ALS mice showed a high NK cell frequency in the spinal cord (Finkelstein et al., 2011). NK cell-derived IFN-γ induces microglia toward an inflammatory phenotype, regulates the release of CCL2, a chemokine that can regulate CNS infiltration, from MNs, and impairs Treg cell migration (Garofalo et al., 2020). More studies are needed.

CONCLUSION

Previous investigations of neuroinflammation in ALS have mainly focused on the relationship between the two immune systems and ALS, respectively. Nevertheless, much less is discussed on the crosstalk between PIS and CIS in ALS, especially the role of the CNS barriers. In this review, we updated the understanding of the relationship between neuroinflammation and ALS. Crosstalk involving central immune cells and peripheral immune cells, CNS barriers, cytokines and chemokines was fully discussed. The dysfunction of all these elements contributed to the non-cellulous death of MNs. Crosstalk plays an important role in the systemic inflammatory milieu in ALS. It should be fully considered for mechanisms and treatment discovery in ALS.

CNS barriers play a crucial role in the crosstalk; thus, they may be a target when optimizing medicine use with ALS. For example, riluzole is a substrate for P-gp and BRCP expressed on CNS barriers so the drug efficacy may be negatively affected (Jablonski et al., 2014). Inhibitors of P-gp have been proven to improve drug delivery in ALS mice (Gil-Martins et al., 2020), but clinical trials should be conducted and more investigations are needed. In addition, a combination of possible CNS barriers-impaired medicine with other therapies may be beneficial. Angiopoietin-1 promotes angiogenesis in the CNS and reduces vascular permeability. The C16 peptide repairs vessels and inhibit transmigration and infiltration of leukocytes without the side effect of systemic immunosuppression. The roles of these two medicines have been well studied in animal models of CNS inflammation (Wu D. et al., 2020), but further experiments

in ALS are needed. Notably, the effect of neuroinflammation is dual, as it exerts a neurotoxic or neuroprotective effect during the disease. In conclusion, normalizing immune crosstalk and homeostasis instead of suppressing inflammation may provide a potential therapeutic target and direction for future study.

AUTHOR CONTRIBUTIONS

WY and JH wrote the manuscript and reviewed the literature under the supervision of DF. XC and ZY drafted the figure and table. ZZ revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by the National Natural Science Foundation of China (Grant Nos. 81873784, 82071426, and 81974197), the Clinical Cohort Construction Program of Peking University Third Hospital (Grant No. BYSYDL2019002), and Beijing Natural Science Foundation (Grant No. 7222215).

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