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Review

The choroid plexus in inflammatory and degenerative diseases of the central nervous system☆

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Supporting the health and function of the central nervous system (CNS), the choroid plexus (CP) not only produces cerebrospinal fluid, but it also facilitates brain–immune interfacing, removes waste, and secretes proneuronal signals. Despite these key physiological contributions, a pathogenic role for the CP in promoting neurologic disease has been relatively underappreciated. Resident CNS cells, including microglia, and peripheral immune cells, such as lymphocytes and macrophages, can interact to promote inflammatory changes within the brain. Such an environment, rich in cytokines and antibodies, can be neurotoxic and produce the symptoms of neuroinflammatory diseases. In other conditions, poorly understood metabolic and cellular disturbances damage neurons and their support cells, such as oligodendrocytes. The progressive loss of functionally intact neuronal networks is responsible for the sequelae of neurodegenerative diseases. Originally described as separate entities, neuroinflammatory and neurodegenerative conditions nevertheless actually share several remarkable similarities. Research indicates that these diverse neurologic pathologies are linked by core CP aberrations, including infiltration by peripheral immune cells, enhanced leukocyte transmigration, paracellular barrier breakdown, synthesis of inflammatory signals, impaired clearance of cerebrospinal fluid neurotoxins, and diminished neurotrophic factor release. This review article highlights recent advances in understanding CP deficits in several prominent inflammatory and degenerative conditions of the CNS. Importantly, the evident intersection between these two categories emphasizes the need to study them in parallel. In doing so, much-needed advances can be made in understanding and managing both neuroinflammation and neurodegeneration.

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Introduction

The brain choroid plexus (CP) is a tubular monolayer of polarized epithelial cells, which surround capillaries formed by fenestrated endothelia. Stromal cells, such as fibroblasts, provide additional structure. Also present are resident immune cells, including macrophages and dendritic cells, as well as central nervous system (CNS) surveilling lymphocytes [1]. The CP primarily functions to filter the blood to produce cerebrospinal fluid (CSF) and to remove harmful molecules from the CNS [2]. These secretory and clearance roles are facilitated by the CP's location within the brain's ventricular system [3].

In healthy individuals, the CSF is comprised of water, electrolytes, macronutrients, proteins, and low levels of immune mediators and cells. The cuboidal epithelial cells of the CP carry out water and solute transport between the serum and the CSF, thus forming the blood–CSF barrier (B-CSFB) and determining the composition of this vital fluid through paracellular, transcellular, and secretory regulation [1]. CP epithelia have a clear polarity that is maintained by adherens and tight junctions anchored to the cellular cytoskeleton [4]. With these junctional complexes, the free paracellular diffusion between the serum and CSF of solutes larger than a few hundred Daltons is prohibited [5]. For reference, interleukins (ILs) tend to be tens of thousands of

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Daltons, and immunoglobulins are hundreds of thousands of Daltons [6]. Even the smallest bacterium is over 200 times too large to pass between CP epithelial cells under normal conditions [7]. Therefore, a healthy CP should allow negligible free paracellular diffusion of harmful products into the CSF.

Regarding transcellular transport, key proteins act at the apical and basal membranes to facilitate the movement of molecules through CP epithelial cells. These include membrane-spanning channels or transporters and vesicular machinery. Activity of membrane channels and transporters, such as organic anion or cation transporters and solute carrier transporters, move moderately sized molecules into the CSF, such as small peptides and saccharides [8]. Larger molecules, such as polypeptides, and those without transporter flux, can be moved across the epithelia through vesicular transcytosis [9]. The vesicular trafficking pathway has been shown to mediate the blood-to-CSF movement of specific peptides, including several hormones and macronutrients [1,8]. While this mechanism enables other epithelial tissues to transport blood born immunoglobulins into luminal fluids [10], similar activity of this pathway has thus far proven difficult to assess in CP epithelia.

Another key function of transcytosis pathways, the CP clears many waste and neurotoxic molecules from the CSF. Oxidative products, cellular debris, excess neurotransmitters, and pathogens are regularly removed from the CSF by the CP epithelia. Membrane channels and transporters, including the ABC transporter family, facilitate many of these housekeeping processes [8,11,12]. Disruption of the normal clearance activity of the CP, therefore, can lead to the accumulation of substrates which promote inflammation and loss of neurons within the CNS.

In addition to transporting blood products, the CP epithelia also synthesize and release vital proteins into the CSF [13]. Importantly, these CP-derived molecules include neurotrophic factors, such as such as brain-derived neurotrophic factor (BDNF), which support the survival of neurons [14]. Additionally, CP epithelial cells can secrete cytokines, such as such as fibroblast growth factor-21 (FGF-21), transforming growth factor (TGF) beta, lipocalin-2 (LCN2), and IL-6 [15]. Based upon its permissive vascular anatomy, the CP is readily exposed to large amounts of systemic blood products; its synthetic functions appear to be responsive to systemic inflammation *in vitro* and *in vivo* [16,17].

Under systemic inflammatory conditions, increased recruitment of immune cells, including lymphocytes, can lead to significant expansion of the resident immune cell population and increased rates of immune invasion into the CNS [18,19]. Immune surveillance entails the migration of peripheral macrophages, dendritic cells, and T cells to the CSF side of the CP to sample for CNS antigens and interact with microglia [20]. While beneficial at low levels, dysregulated surveillance can precipitate a CNS-targeted immune response [21–23].

The other major barrier system of the brain, the blood-brain barrier (BBB), can similarly be impacted by inflammation; however, key physiologic differences indicate that the B-CSFB may be more susceptible to its effects. The BBB is formed by capillary endothelial cells with no fenestrations [24]. The permeability of this endothelial barrier depends more on direct regulation by other cell types, including pericytes and astrocytes [25]. Additionally, the CP epithelia are more metabolically active, having significantly higher secretory activity [8]. Therefore, the CP is more readily exposed to systemic mediators, lacks compensatory regulation, and can directly propagate inflammatory signaling.

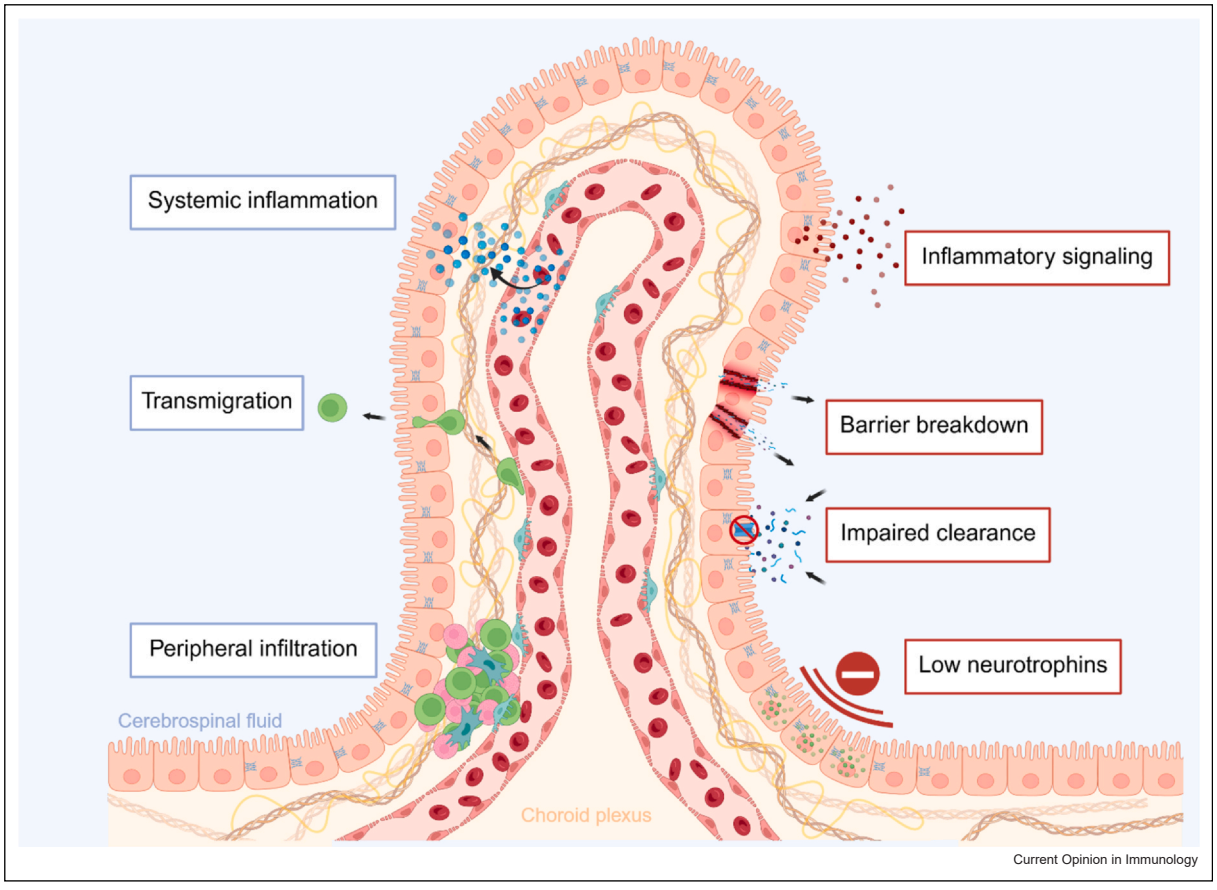
Taken together, dysfunction of the CP's physiology can perturb the normal CNS environment and disrupt neurologic health [20]. Mounting evidence indicates that disruption of vital functions, including the CP's maintenance of CSF homeostasis, role as a brain–immune interface, and secretion of neurotrophic factors [8,13], occurs in numerous neurologic diseases [8] (Figure 1). By enhancing cytokine signaling and the translocation of peripheral immune cells, the perturbed CP appears to promote neuroinflammatory conditions [26,27]. On the other hand, poor removal of harmful CSF substances and reduced secretion of neurotrophic factors by the CP may contribute to the progression of neurodegenerative diseases [14,28].

As the studies substantiating these detrimental roles of the CP in disease pathogenesis have become more numerous, a significant overlap between seemingly disparate diseases has become apparent (Table 1). Neuroinflammatory conditions (e.g. multiple sclerosis [MS], systemic lupus erythematosus [SLE; lupus]) and neurodegenerative diseases (e.g. Alzheimer's disease [AD], Parkinson's disease [PD]), while damaging neurons through unique pathways, may share common perturbations of normal CP function, which promote those mechanisms. This review summarizes recent insights into these and other diseases to highlight the concept that the disruption of the CP may be a fundamental pathogenic step toward fulminant neuroinflammatory and neurodegenerative disease alike.

Neuroinflammation: multiple sclerosis

A prototypical CNS autoimmune condition, MS most commonly presents with motor and sensory disturbances of variable chronicity and severity [29]. Although its initial trigger remains to be discovered, most symptoms of MS occur concurrently with autoreactive lymphocyte infiltration into the CNS and subsequent demyelination

Figure 1



Mechanisms of CP dysfunction in neuroinflammatory and neurodegenerative diseases. Schematic depicting the architecture of the CP, including fenestrated capillaries (red vessel), extracellular matrix (yellow helices), and epithelial cells (orange cell monolayer). Additionally, the diagram depicts the exposures (left; blue boxes) and perturbed functions (right; red boxes) of the CP in the inflammatory and degenerative conditions of the brain described in the article. Image generatedusing Biorender.

[29]. Emerging research into MS assigns pathogenic significance to disruption of the CP [30]. In the experimental autoimmune encephalitis murine model of MS, CD4+ T cells, particularly the autoimmune Th17 subtype, were found to accumulate within the CP before disease manifestations [31]. Similarly, B cells are known to redistribute within the CSF and brain tissue during active MS flares [32]. *Ex vivo* trans-well studies recently demonstrated that MS patient–derived memory B cells readily follow chemokine gradients to cross the CP epithelial barrier [33]. Therefore, the CP seems to serve as a gate of entry for adaptive immune cells that are primed to react to host neuronal epitopes.

Apart from permitting peripheral immune entry, disruption of CSF homeostatic functions appears to occur through CP dysfunction in MS. Enlargement of the CP volume, a purported biomarker of inflammatory dysfunction, can be found in MS [34]. In a cross-sectional In a cross-sectional magnetic resonance imaging (MRI) study of over 100 MS patients, CP enlargement correlated with both the number of demyelinating lesions and overall white matter atrophy, independent of ventricle volume [35]. Failure of remyelination in MS may be predictive of disease outcomes. A recent imaging study found that failure of remyelination occurred most frequently in the periventricular white matter, and failure rates declined as distance from the ventricles increased [36]. Intriguingly, CP enlargement was also found to correlate with lower rates of successful remyelination [36]. T and B cells readily infiltrate and cross the CP barrier in MS. Additionally, a primary disruption of the CP appears to be linked to white matter pathology in MS. Thus, the CP likely plays an important role in the initiation, through lymphocyte infiltration, and progression, through perturbed remyelination, of MS.

Neuroinflammation: systemic lupus erythematosus

Often presenting in women of reproductive age, the multisystem autoimmune condition SLE occurs through

Table 1

Summary of key functional CP disturbances reported in neuroinflammatory and neurodegenerative conditions.

Condition	CP changes					Citation
	Enlargement	Altered function				
		Barrier integrity	Immune interface	CSF homeostasis	Neurotrophic signaling	
Multiple sclerosis	Present; correlates with lesion burden		Th17 infiltration; memory B cell transmigration	CSF-proximity dependent remyelination failure		[31,33,35,36]
SLE	Present; correlates with NPSLE	IgG deposits in the MRL/lpr brain near ventricles; patient CSF contains high levels of serum proteins	Infiltrate forms TLS and brain-specific immune responses driven by BTK and TWEAK among others	CP synthesis of CSF-elevated inflammatory molecules; deficient ABC transporter clearance		[24,41,42,45,49,51,52,55]
Infections and the environment		Cytoskeletal and junctional complex disruption	Upregulated interferon signaling and microglial stimulation			[57,84]
Normal aging	Present; increased volume with older age			Infusion of young mouse CSF ameliorated memory deficits in old mice	Declining synthesis of BDNF and Klotho	[65–68]
ALS	Present; correlates with symptom severity	High CSF:serum albumin quotient; reduced tight-junction integrity	Macrophage infiltration; peripheral inflammation correlates with CP volume			[71–73]
AD	Present; correlates with plaque burden and symptom severity	Loss of microstructural integrity correlates with serum neuronal protein levels		Patient CSF proteomes contain immune mediators and remodeling factors	Downregulation of BDNF in those patients with prominent CP enlargement	[76–79]
PD	Present; correlates with higher rates of executive dysfunction			Diminished CSF flow linked to higher plaque burden		[82,83]

BTK, Bruton's tyrosine kinase.

a breakdown of immune tolerance to self-antigens and subsequent expansion of autoreactive T cells and B cells, resulting in high circulating autoantibody levels to nuclear and other cellular antigens [37]. While cardiovascular and renal involvement represent the most common causes of mortality in lupus, significant morbidity is associated with neuropsychiatric involvement [24]. Many SLE patients, estimated as to read 20–40% or more, experience concurrent disturbances in cognition, memory, and/or mood regulation, collectively termed neuropsychiatric lupus (NPSLE). Loss of neurons and white matter irregularities in the brain are known to accompany these symptoms [38,39]. While the cause of this pathology is only beginning to be uncovered, recent evidence substantiates a prominent role of the CP similar to that seen in MS.

Enlargement of the CP was found in SLE patients versus healthy controls, and the most prominent enlargement was detected in those with NPSLE [40]. Immune cells are known to infiltrate the CP in NPSLE [24]. As described in this article, several inflammatory and degenerative neurologic diseases have abnormal immune cell infiltration into the CP. However, those occurring in lupus stand apart due to their complex composition and functional organization. In our studies of NPSLE, we prioritized the investigation of the etiology and pathologic impact of this CP infiltrate in the most robust murine model of this particular disease manifestation, the MRL-lpr/lpr (MRL/lpr) mouse.

To characterize the composition of the CP infiltrate over time, single-cell transcriptomes were generated from the CP infiltrate in both young and old MRL/lpr lupus mice. A multitude of immune and stromal cell clusters were identified. One prominent feature was the diversity of T cell phenotypes seen, including a subset possessing T cell receptors specific for myelin basic protein [41]. Thus, there is an autoreactive pool of lymphocytes that are local to the CP and which form a brain-specific response. Additional flow cytometry studies detected the presence of follicular-type helper T cells and a diminished content of regulatory T cells within the CP infiltrate [42]. Dysregulated balance of these T cell subtypes further indicates a shift toward a pathologic adaptive immune response.

Adoptive transfer of CP-infiltrating T cells intrathecally to immunodepleted MRL/lpr lupus mice worsened cognitive deficits associated with murine lupus, compared to transfer of splenic T cells or sham injections [43]. A similar study found that T cell neurotoxicity may depend on interferon-γ activation of microglia [44]. These T lymphocytes readily cross from the periphery into the CP, having been detected on the CSF-facing side of the barrier [44]. Thus, T cells exhibit pathogenic potential in the development and severity of NPSLE, although certainly additional immune cell types besides T cells may help mediate these effects.

The immune infiltrate of the CP contains more than just T cells. Dendritic cells, macrophages, and B cells also appear in these aggregates [45]. Since follicular T cells were also present, we wondered if these CP infiltrates might organize into germinal center–like structures. Indeed, the CP of murine MRL/lpr mice contained tertiary lymphoid structures (TLS), wherein antigen presentation and cytokine signaling could accomplish B cell education, priming the production of brain-specific autoantibodies [45].

Several key molecules appear to regulate the lymphoid organization in the CP in NPSLE mice. Blockade of Bruton's tyrosine kinase using a small molecule inhibitor reduced the accumulation of T cells, B cells, and macrophages within the CP [46] and improved cognitive function. Similarly, the lymphocyte-recruiting chemokine CXCL13 was also found to mediate features of NSPLE [47], with intraperitoneal or intrathecal injection of anti-CXCL13 antibodies significantly ameliorating cognitive and affective behavioral features in lupus mice. Interestingly, though, the lymphocytic infiltrate within the CP was not disrupted in anti-CXCL13 treated mice despite blocking this potent chemoattractant.

Inhibiting TNF-like weak inducer of apoptosis (TWEAK) signaling, an inflammatory cytokine with effects on the innate and adaptive immune system, diminished NPSLE-like symptoms in lupus mice [48]. With roles in T cell recruitment and B cell maturation, knocking out the TWEAK receptor Fn14 in MRL/lpr mice reduced the CP infiltrate. Notably, this effect was also accompanied by a reduction in neuron degeneration and hippocampal gliosis [49]. Thus, several signaling molecules and pathways play a role in the pathogenesis of NPSLE, with variable effects on the CP infiltrate. To further elucidate the origin of this infiltrate, we also performed bone marrow transplants from nonlupus mice to immunodepleted MRL/lpr lupus mice [50]. Interestingly, both CP infiltration and abnormal neurobehavioral features persisted in these mice, indicating that systemic inflammation may not be required for the emergence of either manifestation. Perhaps, the CP infiltrate is driven more by an intrinsic perturbation in the CP or CNS, rather than arising from systemic inflammation. But whatever the trigger of immune infiltration into the CP, CP TLSs possess the ability to promote brain-specific immune responses and are closely related to the debilitating manifestations of NPSLE.

Beyond acting as a brain–immune interface, disruption of the CP epithelia themselves may further worsen NPSLE-associated neuroinflammation. We identified a perturbed CSF composition as a key factor that can promote an inflammatory CNS environment. Quantification of over 1000

unique proteins in the CSF of NPSLE patients identified numerous potential biomarkers (i.e. M-CSF) of the disease, of which a subset was found to be also overexpressed in the CP [51]. Therefore, inflammatory molecules permeate the CSF in NPSLE, and the dysregulated CP may be producing mediators that promote brain pathology.

Among those potential mediators, IL-6 emerges as the cytokine most commonly reported to be elevated in NPSLE serum and CSF [52]. Lupus mice show similar elevations of intrathecal IL-6 [53]. Inflammatory cytokines, like IL-6, further have the capacity to disrupt epithelial cell functions [54]. For this reason, we recently explored the CP-altering capacity of the cytokine. Using CP epithelial spheroids from lupus mice, the lack of IL-6 signaling was found to increase the luminal content of exogenous fluorescent tracers. Moreover, IL-6 inhibited the clearance of ABC transporter substrates from the CSF-like fluid within the spheroid vacuole [55]. The high IL-6 environment in lupus and NPSLE inhibits these vital transporters; therefore, it could promote the accumulation of neurotoxic ABC substrates, such as leukotrienes, and worsen neuroinflammation. In summary of these studies of the CP in SLE, a robust immune cell infiltrate, dysregulated synthetic activity, and hampered clearance are fundamental alterations to CP function that may underlie key features of NPSLE.

Neuroinflammation: infections and environmental exposures

A variety of pathogens impact the CNS, often by directly invading the brain and causing inflammatory dysfunction. Similar to autoimmune conditions, neurotropic infections appear to disturb the CP and its typical functions [56]. Notably, Neisseria meningitidis, a potent cause of bacterial meningitis, can infect CP epithelial cells and induce cytoskeletal and cellular junction changes, which together potentially disrupt the barrier integrity of the B-CSFB [57]. SARS-CoV-2, the viral cause of COVID-19, possesses high tropism for CP epithelia due to their ACE2 expression. Upon infection of human-derived organoids, the virus also induced barrier-disrupting microstructural changes in CP epithelia [58]. Similarly, infection with the parasite *Toxoplasma gondii* induced the loss of CP epithelial tight junctions and upregulation of matrix-remodeling enzymes, changes that occurred early in infection and persisted throughout the disease [59].

Beyond promoting pathogen invasion through the blood–CSF barrier, infections appear to also promote the direct activation of inflammatory pathways by the CP epithelia. For example, the single-cell transcriptomes of CP epithelia in patients infected with SARS-CoV-2 revealed an inflammatory signature. Within this CP epithelial signature, upregulated interferon signaling and upstream activators of microglia corresponded to pathologic signatures within the frontal cortex [60]. A common theme among these neuroinflammatory conditions, is that disruption of the CP in infections can lead to increased permissiveness as well as disturbed epithelial signaling via the CSF. As we will see, these features also occur in age-related and pathologic neurodegeneration.

Researchers have begun to appreciate the emerging influence of environmental exposures, including novel toxins and synthetic molecules, on epithelial barriers throughout the body. Several neuropsychiatric conditions discussed in the present article have recently been shown to involve dysregulation of the gut epithelial barrier and increased neuroinflammatory signaling [61]. The CP as well appears to be susceptible to pollutants. Specifically, the sequestration of heavy metals like cadmium or lead, which is an essential CNS-protecting function of the CP, can disrupt normal functions of the epithelia over time [62]. While future work is needed to uncover specific physiological alterations, environmental exposures potentially modulate B-CSFB properties, compromising its integrity in inflammatory conditions.

Neurodegeneration: aging and stroke

While increasingly thought to involve inflammatory changes, neurodegenerative diseases broadly involve the direct loss of viable neurons through a multitude of intracellular and extracellular insults [63]. Moreover, these changes are not regarded as the immediate result of the interaction of immune cells or antibodies with neurons, as is fundamental to many neuroinflammatory conditions. However, recent work in several conditions has uncovered that disruption of CP function in neurodegeneration may closely resemble that of the previously discussed inflammatory conditions.

Normal aging is associated with the gradual loss of cerebral neurons, whereas vascular insults, such as ischemic strokes, cause a more sudden loss of gray matter [63,64]. Adult neurogenesis, or the generation of new neurons from neuroblasts located within specific niches, is thought to contribute to the slowing of age-related decline and recovery from injury. In a mouse model with an inducible ablation of the CP, loss of CP function reduced the number of neuroblasts and their migration to ischemic stroke sites [65]. Thus, the CP appears to exert neurotrophic effects, likely through the release of factors promoting neuron health and recovery. Under aging conditions, the CP undergoes structural and metabolic changes, which likely hinder its typical secretory functions [66]. As such, the release of neurotrophic factors, including FGF-17, BDNF, IGF, and Klotho, may decline with age [67].

Even under normal conditions, aging is also associated with increased CP volume in humans [68]. Additional

experiments found that the infusion of young mouse CSF into the ventricles of aged mice improved memory functions. Specifically, hippocampal oligodendrocytes, the myelinating cells of the CNS, became more numerous in the aged mice once exposed to young CSF [69]. A similar inability to maintain myelination was seen with CP changes in MS. Thus, the loss of the normal beneficial effects of the CP on the brain links age-related decline with neuroinflammatory conditions.

Neurodegeneration: amyotrophic lateral sclerosis

Occurring through an unknown mechanism, amyotrophic lateral sclerosis (ALS) rapidly progresses to paralysis of multiple muscle groups due to the loss of motor neurons. ALS patients, who tend to be a few decades younger than those with other neurodegenerative diseases, often experience bulbar symptoms (i.e. dysarthria and dysphagia), declining fine and gross motor strength, and the eventual loss of respiratory function [70]. In a cross-sectional examination of 155 ALS patients and 105 healthy controls, CP enlargement was found among the ALS patients. Moreover, larger CP volumes corresponded to higher CSF/serum albumin quotients, a proxy of brain barrier dysfunction, and worse clinical symptoms of the disease [71]. Postmortem analysis of human CP in ALS individuals found a loss of tight-junction integrity, potentially explaining the increased entry of serum solutes into the CSF [72].

Interaction of the peripheral immune system with the CP also appears to be a prominent feature of ALS. Invasion of macrophages into the tissue has been found on postmortem analysis [72]. Furthermore, serum inflammatory protein levels correlated with CP changes. Specifically, ALS patients had elevated serum cytokine and chemokine levels, of which CRP, IL-6, and CXCL10 predicted increased CP volumes [73]. Not typically regarded as an inflammatory condition, ALS demonstrates how the loss of CP barrier integrity and dysfunction in the brain–immune interface can unexpectedly blur the distinction between a neurodegenerative and neuroinflammatory condition.

Neurodegeneration: Alzheimer's disease

During the progressive course of AD, neurons are thought to be lost through a combination of protein misfolding, glial reactivity, and decline in neurotrophic health [74,75]. Occurring most frequently in elderly patients, the cumulative effect of this pathology is an early decline in memory and cognition with personality and perceptive changes appearing late in the disease course [74]. As in nearly all the previously discussed conditions, AD patients demonstrate enlargement of the CP. Using MRI and positron emission tomography to detect amyloid protein plaques, this CP enlargement was found to correlate with overall plaque burden and worse cognitive function [76]. A recent study revealed that loss of microstructural integrity correlated with serologic signs of AD pathology (i.e. elevated neuronal protein levels) [77]. In fact, these changes existed in this longitudinal aging cohort before clinical AD manifestations. Among the identified serum biomarkers, elevated Among the identified serum biomarkers, elevated glial fibrillary acidic protein, an indicator of glial reactivity, positively correlated with CP volume [77].

Using an amyloid precursor protein knock-in mouse model of AD, the proteome of CP epithelial cells and the whole CSF proteome were found to significantly differ from control mice, and follow-up analyses found remarkable overlap with the human AD CSF proteome [78]. These proteomic changes are largely related to dysregulation of the extracellular matrix and immune system: two pathways readily altered in neuroinflammatory conditions with CP pathology. Another proteomic profiling study sought to subcategorize AD patients by the contents of their CSF [79]. Among the five diagnostic clusters, one was defined by markers of CP dysfunction, microglia activation, and immune cell functions. Similarly, this cluster of patients had the largest CP volumes and most severe cerebral atrophy. This latter effect was potentially related to the downregulation of neurotrophic factors, including BDNF, which also characterized this CP cluster [79]. While it remains to be seen if CP dysfunction is universal in AD, those patients with CP dysfunction appear to exhibit some of the most exaggerated pathological changes associated with AD.

Neurodegeneration: Parkinson's disease

Another classic example of progressive neurodegeneration, PD owes its progressive, debilitating motor symptoms to the loss of dopaminergic neurons in the basal ganglia due to misfolded protein (i.e. tau) accumulation [80]. This dysfunction produces the stereotypical presentation of resting tremor, bradykinesia, and rigidity, a highly morbid constellation of symptoms [81]. However, Parkinson's patients often develop neurocognitive symptoms as well. Once again, the CP appears to modulate the severity of this neurodegenerative condition. In a longitudinal study of over 200 newly diagnosed PD patients, larger CP volumes corresponded to a higher rate of developing Parkinsonian dementia and negatively correlated with executive function [82]. Similarly, a diminished level of dopaminergic activity in the nigrostriatal pathway of the basal ganglia was found to correlate with CP enlargement, motor dysfunction, and clinical severity [81].

Recent insights offered a potential explanation to this link between CP dysfunction and PD pathology. Using diffusion-weighted MRI in 27 PD patients and 32 healthy controls, the level of CSF flow was found to be decreased in PD patients. Further analysis found that

diminished perfusion of the CP corresponded to these poor CSF dynamics [83]. This group further proposes that stasis within the brain ventricles could reduce the clearance of protein plaques in PD. Additional studies are needed to assess this hypothesis, but perturbation of the CP and CSF homeostasis is evident in the disease. Moreover, the clearance functions of this system in maintaining brain health appear deficient in PD, as was seen in the neuroinflammatory condition NPSLE.

Concluding remarks

Multiple pathways of CP-mediated changes appear to occur with striking similarity in neuroinflammation and neurodegeneration alike. The CP enlarges, immune cells infiltrate, synthetic functions shift, and clearance activity declines. Taken together, dysfunction within the CP epithelia leads to reduced barrier integrity, enhanced brain–immune interfacing, deficient CSF homeostasis, and diminished neurotrophic signaling. Whether a primary cause or secondary to the separate disease processes, the altered CP appears to worsen the pathophysiologic progression of multiple debilitating neurologic diseases.

As this theory of shared CP disruption represents an emerging concept, much of the early data here presented involves correlational evidence. While this is a vital first step in establishing a potentially novel unified understanding of CP pathology, mechanistic studies are still needed to truly assess its validity. Following such investigations, the emergence of CP-targeted therapies, including the blockade of systemic or intrathecal factors to limit inflammatory changes, could represent a much-needed advance in the treatment of multiple diseases. Moreover, the similarities observed between neuroinflammation and neurodegeneration, two classically distinct categories of disease, emphasize the need to study inflammatory and degenerative processes in the brain as a continuum, or perhaps two sides of the same coin.

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Declaration of Competing Interest

None of the authors have competing interests, financial or otherwise.

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- • of special interest
- • of outstanding interest

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