

REVIEW

The cribriform plate: A dynamic central nervous system–immune hub

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Olfactory nerve bundles exit the brain through the cribriform plate (CP) with a rich perineural microenvironment (cpPME). This microenvironment facilitates interactions between cerebrospinal fluid, blood vessels, bone marrow, and lymphatic vessels. The immune niche of the cpPME changes in response to inflammation caused by stroke, autoimmunity, infection, and Alzheimer's disease. Neuroinflammation at the CP results in dysfunction of olfaction that might have diagnostic value in neurological disorders. Additionally, the proximity of the CP to the nasal mucosa allows targeted therapeutic interventions. A thorough understanding of the cpPME is essential for designing innovative diagnostics and treatments for neuroinflammatory diseases.

Introduction to central nervous system (CNS)–immune hubs

While the immune system is highly decentralized, it still integrates information and coordinates responses within distinct immune hub regions like the spleen and lymph nodes. The CNS is also organized into distinct hubs where neural and immune systems converge (Rustenhoven et al., 2021; Fitzpatrick et al., 2024). One immune hub is the meninges, where assembly of immune cells at the meningeal interfaces performs regulatory functions at the dural membrane (known as dural-associated lymphoid tissue [DALT]) and within the subarachnoid space, where cerebrospinal fluid (CSF) interacts with immune cells (Zanluchi and McGavern, 2024). Other immune hubs are associated with the choroid plexus and perivascular spaces of the brain and spinal cord. Emerging principles indicate that under homeostatic conditions, CNS–immune hubs promote immune tolerance and regulation, while in disease states, these hubs can be sites of dysregulation leading to neuroinflammation. The integration of peripherally connected lymphatics into these immune hubs helps coordinate inflammatory responses through antigen drainage into the cervical lymph nodes (CLNs) (Aspelund et al., 2015; Louveau et al., 2015; Louveau et al., 2018).

Investigating these CNS–immune hubs during neuroinflammation not only provides a framework to study the pathogenesis of diseases like multiple sclerosis (MS), Alzheimer's disease (AD), brain infections, and brain cancer, but might also be a therapeutic target to better treat these diseases.

While CSF drainage via the dorsal dural route has been the focus of many studies, lymphatic drainage and immune regulation at the cribriform plate (CP) have been largely overlooked. In this review, we will focus on one CNS–immune hub, the cribriform plate perineural microenvironment (cpPME), and highlight recent advances on how it participates in neuroinflammatory disease. We argue that the cribriform lymphatics, local skull bone marrow, and broader immune environment associated with the olfactory nerve bundles are crucial for CSF efflux and neuroimmune surveillance making it a novel axis to treat CNS neuroinflammatory diseases. Distinct myeloid and lymphoid cell populations localize to perineural niches of olfactory nerve bundles, including lymphatic vasculature, during neuroinflammation, indicating a specialized and responsive immune surveillance pathway (Hsu et al., 2022; Laaker et al., 2025; Xin et al., 2025). Ultimately, we argue that better understanding of CSF drainage sites, such as the cpPME, can lay the foundation for new CNS-targeting immunotherapies.

Anatomy of the cpPME

The CP is a portion of the ethmoid bone that contains foramina where blood vessels and olfactory nerve bundles (fila olfactoria) along with their surrounding environment pass from the olfactory bulb into the underlying olfactory mucosa (Fig. 1 B). Thus, the CP provides an essential boundary and link between the CNS and the periphery as skull-traversing olfactory nerves

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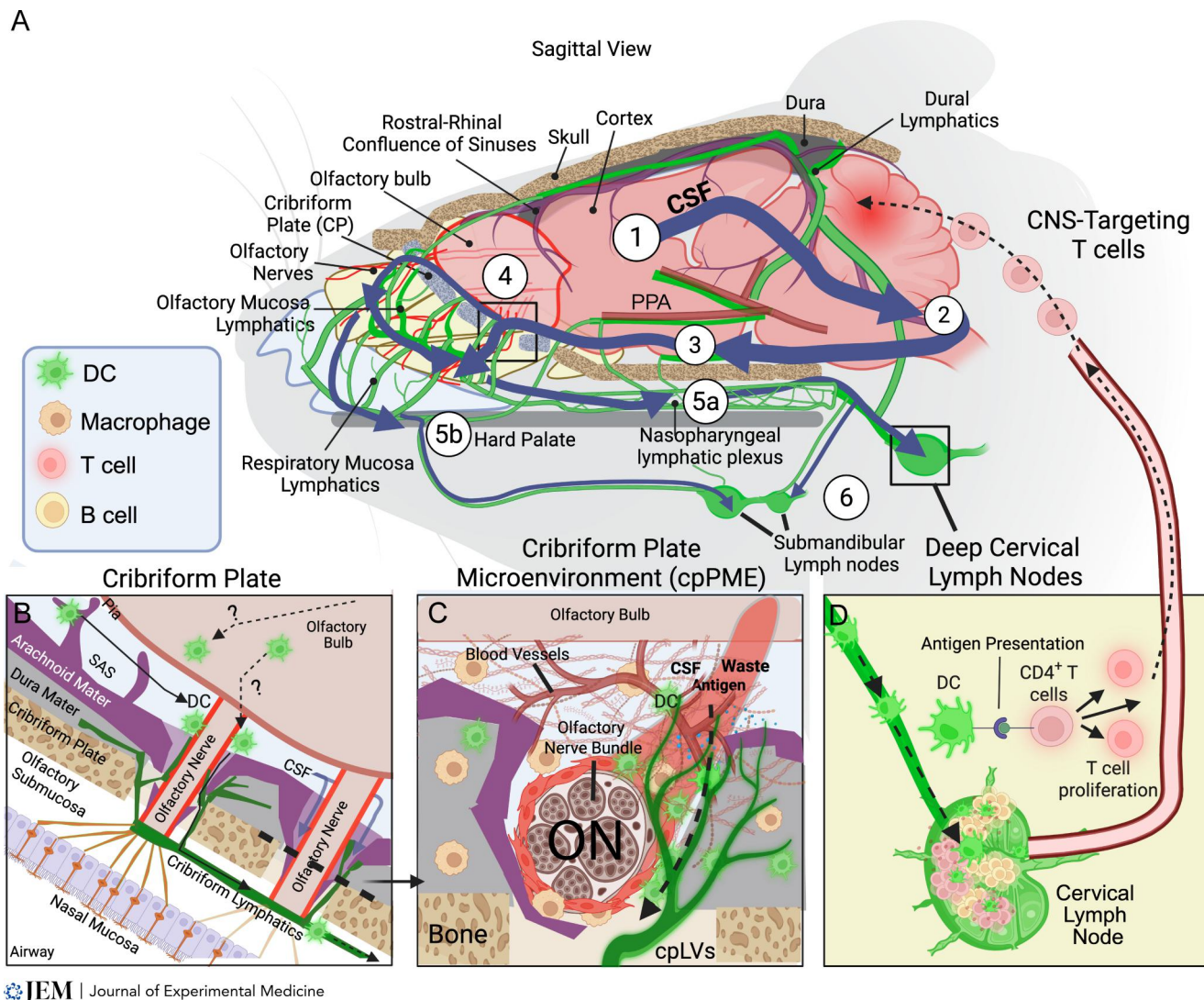


Figure 1. Proposed CSF drainage pathway through the murine CP. (A) Sagittal view of the mouse brain showing CSF circulation (blue) and proposed outflow across the CP to nasal soft tissue and cribriform/nasal lymphatic vessels (green) that drain into CLNs (Jin et al., 2025; Yoon et al., 2024; Decker et al., 2022; Papadopoulos et al., 2025). Pathways include the following: (1) CSF is secreted from choroid plexus; (2) CSF exits from ventricles into subarachnoid space, (3) flows along base brain, and (4) effluxes through the CP lymphatics near olfactory nerve bundle environment; and (5a) olfactory mucosa lymphatics drain into nasopharyngeal lymphatic plexus and into (6) CLNs for antigen presentation and T cell activation. Alternatively, deep respiratory mucosal lymphatics (5b) drain through the hard palate and nasal sidewall to submandibular lymph nodes (or superficial CLNs) (6). **(B)** Sagittal schematic of the CP region highlights olfactory nerve bundles (fila olfactoria), arachnoid extensions of the subarachnoid space, and lymphatics that receive antigens and immune cells. **(C)** cpPME contains olfactory nerve (ON) bundles ensheathed by discontinuous arachnoid-like tissue, DCs, macrophages, and cpLVs that sample CSF, waste, and antigens. **(D)** Antigen-loaded DCs traffic to CLNs, where they present CNS antigens to CD4⁺ T cells, driving proliferation of CNS-targeting T cells that can migrate to the brain and influence neuroinflammation. Panels A and B are modified from Laaker et al. (2023).

enable sensory signals to reach the olfactory bulb. Additionally like the brain which is covered with three meningeal layers (pia mater, arachnoid mater, and dura mater), each olfactory nerve bundle is similarly wrapped with a pial-like membrane and further enclosed by the arachnoid mater and, at certain regions, portions of dura mater. As each nerve bundle passes through the CP, an extension of the CSF-filled subarachnoid space also extends alongside it, allowing olfactory nerve bundles to remain in continuous contact with CSF (Fig. 1 C) (Bradbury et al., 1981; Brierley and Field, 1948; Proulx, 2021; Walter et al., 2006). The drainage of CSF is important for several reasons: (1) it allows immunological sampling of antigens and immune cell trafficking

to ensure proper homeostasis; (2) it provides routes to facilitate drainage of excess fluid or edema within the brain, avoiding lethal elevation of intracranial pressure; and (3) it facilitates transport of nutrients and disposal of metabolic waste.

In mice, evidence supports that the E-cadherin⁺ arachnoid layer is discontinuous near olfactory nerve bundles, enabling CSF access to the plexus of initial lymphatic vessels at the CP (Spera et al., 2023; Hsu et al., 2022; Xin et al., 2025). It is still unclear whether these vessels should be defined as “meningeal,” but several studies have documented that Prox1⁺ intracranial lymphatic vessels in the cribriform dura traverse the murine CP, linking meningeal and nasal lymphatic networks (Fig. 1, B and C)

(Yoon et al., 2024; Jin et al., 2025). Thus, this anatomical conformation enables lymphatic drainage of CSF, waste, cells, and antigen into the peripheral lymphatic system (Spera et al., 2023; Hsu et al., 2022), ultimately draining contents into the deep and superficial CLNs along circuits where it can inform adaptive immune responses (Fig. 1 D) (Yoon et al., 2024; Jin et al., 2025; Papadopoulos et al., 2025). Importantly, there is still debate about the relevance of meningeal connected lymphatics, which traverse the CP and their contribution to overall CSF outflow observed in the nasal region (Papadopoulos et al., 2025; Jacob et al., 2022). However, under the framework outlined in Spera et al., draining CSF is proposed to remain in close contact with the olfactory nerve bundles until it reaches regions adjacent to lymphatic vessels, which may be located either (1) on the CNS side of the CP, (2) along the nerve bundles as they traverse the bone (inside the skull), or (3) at points underneath the CP within the nasal submucosa (Spera et al., 2023). This proposed relationship puts the regions surrounding the olfactory nerve bundle as the anatomical backbone, which facilitates drainage to lymphatics across the CP region.

To gain a deeper understanding of the anatomical features of the CP, we created a series of reconstructed murine sections using Lyve-1, a lymphatic marker, and podoplanin, which serves as both a lymphatic and a meningeal marker. We demonstrated how Lyve-1⁺ regions interface with circular cross-sectioned olfactory nerve bundles across the CP in consecutive coronal sections (Fig. 2, A–C). At more rostral sections, portions of ethmoid bone marrow extend into the CP (Fig. 2 D). In contrast, deeper into the brain, lymphatic vessels on the CNS side of the CP exist between olfactory bulbs that are closely associated with midline-traversing nerve bundles (Fig. 2, E and F), highlighting distinct structural relationships across regions. While there is increasing understanding of the cribriform pathway in mice, the complete cribriform-to-nasal lymphatic pathway in humans is not fully mapped. However, postmortem tracer studies point to lymphatic drainage alongside olfactory nerve bundles into the nasal submucosa (Johnston et al., 2004). Electron microscopy has confirmed that humans possess Lyve-1⁺ and AQP1⁺ lymphatic vessels along the epineurium, the outermost sheath of olfactory nerve bundles (Furukawa et al., 2008). Additionally, live imaging supports the CP as a drainage site for CSF in humans (Zhou et al., 2022; de Leon et al., 2017). As we will discuss in the next section, CSF efflux across this unique anatomical region empowers the cpPME to coordinate with the periphery and influence brain homeostasis.

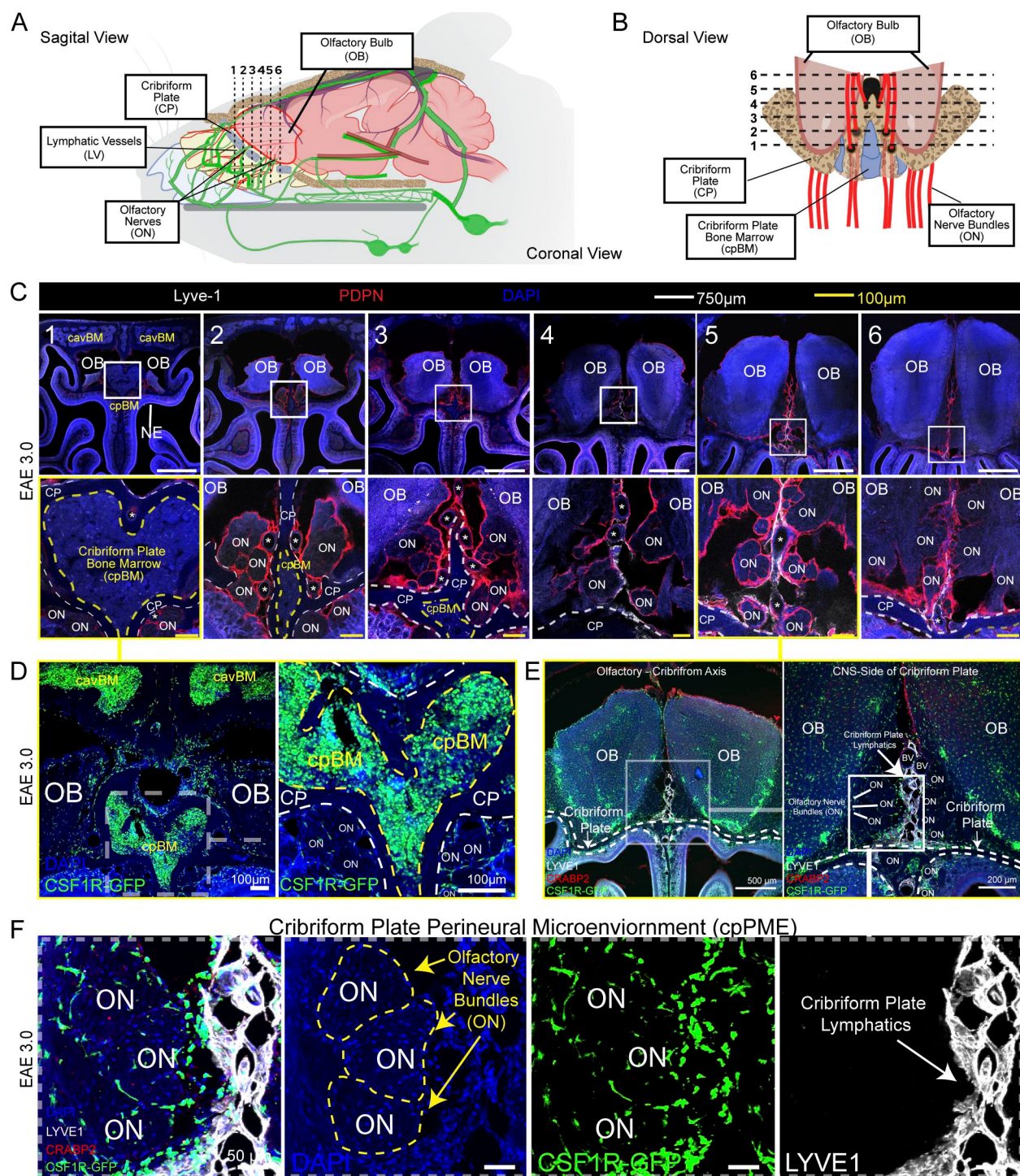
The dynamic pipes and plumbers at the CP

As the CSF is continuously produced at the choroid plexus, it is generally accepted that it must also be continuously drained to maintain intracranial pressure equilibrium (Bothwell et al., 2019). CSF efflux through the CP has been demonstrated across several species including humans (de Leon et al., 2017; Zhou et al., 2022), macaque monkeys (Jin et al., 2025), sheep (Johnston et al., 2004; Mollanji et al., 2001), crocodiles (Dille et al., 2025), and rodents (Papadopoulos et al., 2025; Decker et al., 2022; Ma et al., 2019b; Ma et al., 2017; Yoon et al., 2024;

Jin et al., 2025; Hsu et al., 2022; Hsu et al., 2019; Norwood et al., 2019; Lilius et al., 2023; Kida et al., 1993). In mice, a time-lapse movie of low-rate gadolinium infusions into the lateral ventricles of the brain clearly highlights how CSF moves from the ventricles, along the base of the brain, and finally out through the CP into nasal regions within 30 min (Decker et al., 2022). In agreement with this, intraventricular injections of fluorescent ovalbumin (OVA-647) were shown in decalcified sections to accumulate around olfactory nerve bundles above and beneath the CP in Prox1⁺ initial lymphatic vessels (Decker et al., 2022).

In mice, this pathway of CSF outflow at the CP creates an immunological chokepoint for dynamic fluid and waste drainage of the CNS. During diseases such as bacterial meningitis, MS, and stroke, there is often an increase in the amount of fluid and inflammatory debris that has to be drained and processed (Hoffman and Joerg Weber, 2009; Murthy, 2005). We propose that local and recruited immune cells are key to maintaining homeostasis at the cpPME by sampling draining fluid and antigens to coordinate responses to pathogens, enhancing lymphatic vasculature function for improved drainage, preventing blockages, surveilling antigen, and reshaping the immune regulatory environment. In agreement with this, CP lymphatic vessels (cpLVs) have been shown to undergo lymphangiogenesis in animal models of ischemic stroke (Choi et al., 2025) and MS (Hsu et al., 2022; Hsu et al., 2019). Similar to proliferating lymphatic vessels in the periphery, cpLVs are associated with increased populations of CD11b⁺ VEGF-C producing myeloid cells, which adhere to the lymphatics and promote lymphatic expansion through VEGFR-3 expressed on cpLVs (Fig. 3) (Hsu et al., 2022; Choi et al., 2025). Immune cells like dendritic cells (DCs) and macrophages function as “plumbers” altering the cpPME through their secreted factors and binding interactions with lymphatic vessels.

In addition to increasing the size of the lymphatic pipes, it is also supported that these immune cell plumbers may help process or “unclog” debris and sample antigen. Our lab has shown that cells positioned along cpPME have access to intracranially injected fluid, beads, and even bacteria (Laaker et al., 2025). During experimental autoimmune encephalomyelitis (EAE), a murine model of MS, inflammatory deposits of fibrin aggregate at various CSF drainage sites including at the CP (Xin et al., 2024). During EAE, the accumulation of fibrin precedes the arrival of CCR2⁺ immune cells to the CP, suggesting that immune recruitment to cpPME may be a reaction to the presence of this product (Xin et al., 2024). Fibrin can stimulate TLR4 and CD11b triggering a pro-inflammatory immune response (Smiley et al., 2001; Altieri et al., 1990; Dean et al., 2024). Interestingly, while spinal outflow is potentially blocked by fibrin accumulation, the fluid outflow is maintained at the CP (Xin et al., 2024). Our lab has provided evidence in the APP/PS1 mouse model of AD that amyloid-beta (A β) can also accumulate at the cpPME along CSF-interfacing regions including cpLVs and is also associated with an amyloid-associated immune response (Vrba et al., 2025, Preprint). Together, these studies point to fluid, antigen, and waste accumulation at the cpPME and a reactive population of immune cells, which interface with lymphatic endothelial cells (LECs).



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Figure 2. Serial reconstruction of the murine cpPME during neuroinflammation. (A and B) Schematics of the mouse head showing CP, ONs, olfactory bulb (OB), nasal epithelium (NE), and lymphatic vessels (LV), with cpBM positioned near olfactory foramina. (C) Coronal sections from EAE mice (day 18) reveal Lyve-1⁺ lymphatics (white), podoplanin/PDPN meninges + lymphatics (red), and DAPI⁺ nuclei (blue) across six rostral-to-caudal planes (1–6) of the OB–CP interface. CP = white dotted line. * = blood vessels. Scale bars = 750 μ m (top row), 100 μ m (bottom row). (D) CSF1R-eGFP reporter mice show myeloid cells (green) inside cpBM, clustering around ON bundles, and lymphatic zones during EAE. Scale bars = 100 μ m. (E) Low-magnification view of the OB–CP axis reveals CP LYVE-1⁺ lymphatics adjacent to ON bundles. Scale bars = 500 μ m (left panel), 200 μ m (right panel). (F) High-resolution images of cpPME depicting ONs surrounded by LYVE-1⁺ lymphatics and by CSF1R-eGFP⁺ immune cells. Yellow dotted lines = outline of circular cross-sectioned ONs. Scale bars = 100 μ m. Figure adapted from Laaker et al. (2025) (Fig. S3, A–C; and Fig S4, A and B).



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that recruit DCs, monocytes, and T cells. M2 macrophages in perineural niche can contribute tolerogenic signals (IL-10, TGF- β , PD-L1), while Th1 cells provide inflammatory cues (IFN- γ), which drives immunoregulatory remodeling including upregulation of PD-L1 and MHC-II on immune cells and lymphatic vessels. Bone marrow niches undergoing elevated myelopoiesis within the skull connect to olfactory nerve bundles through channels, potentially supplying immune cells to nearby regions.

Importantly, numerous studies in the periphery have shown that LECs are not merely passive conduits for fluid transport, but also actively regulate leukocyte function through direct immune cell cross-talk (Takeda et al., 2019). For example, in the lymph node LECs act as long-term antigen archives after vaccination or viral infection, capturing antigen and enhancing memory T cell-mediated immunity (Tamburini et al., 2014; Sheridan et al., 2024, Preprint). Under stimulation of IFN- γ , lymphatic vessels in the periphery have been shown to upregulate regulatory proteins like programmed death ligand 1 (PD-L1) and antigen-presenting machinery like MHC-II (Gkountidi et al., 2021; Lane et al., 2018; Dieterich et al., 2017). By expressing PD-L1, LECs can interact with programmed death-1 receptors on T cells, delivering inhibitory signals that dampen T cell activity and foster a tolerogenic environment (Tewalt et al., 2012; Cohen et al., 2014). LECs have also been shown to secrete CSF1, directly promoting survival of tissue-resident macrophages (Mondor et al., 2019), making LECs versatile modulators of their broader immune environments.

Similarly, our lab has shown that the cribriform lymphatic region is more than a site of fluid regulation and dynamically alters during neuroinflammation, upregulating leukocyte attractants like CCL19, CCL2, CCL5, and leukocyte adhesion molecules like VCAM-1 (Hsu et al., 2019, 2022). Additionally, we showed increased numbers of T cells, macrophages, and primarily DCs are actively engaged in binding interactions with cpLVs during EAE (Hsu et al., 2022). Analogous to peripheral lymphatic vessels, cpLVs also exhibited antigen processing and presenting capabilities and capturing and archiving CNS-associated antigens, storing them for presentation to T cells via MHC-II (Fig. 3) (Hsu et al., 2022). Our research has identified an IFN- γ -dependent mechanism driving the upregulation of PD-L1 on cpLVs, enabling them to dampen excessive T cell responses (Hsu et al., 2022). Together, these findings position cpLVs and its surrounding niche as active recruiters and shapers of the immune landscape, tilting it toward immunosuppression in autoimmunity but potentially relevant in other CNS diseases as well. We hypothesize that upstream immunomodulation of the cpPME represents a unique leverage point to influence downstream lymph nodes and provides a framework that could inform therapeutic strategies for inflammatory conditions of the CNS.

Origin of CP immune cells

The origin of immune cells that engage in cross-talk with the cpPME is key to disease pathogenesis and therapeutic intervention. Evidence suggests that immune cells at the cpPME are a combination of resident, peripheral blood-derived, CNS-emigrating, skull bone marrow-derived, and nasal submucosa-derived populations. Thus, the cpPME likely supports a diverse hub of various immune cell inputs and interactions in the cpPME niche (Fig. 3).

Resident populations

Evidence supports that the olfactory nerve bundles have a resident population of perineural myeloid cells. Smithson and Kawaja noted monocyte lineage (Iba1⁺) cells present around olfactory nerve bundles interfacing with nerve fibroblasts even in healthy mice (Smithson and Kawaja, 2010). CX3CR1-expressing macrophages are also observed in perineural regions during healthy conditions (Xin et al., 2025; Xin et al., 2024). Additionally, steady-state populations of CSF1R and CD11c-expressing cells exist in the cpPME under normal conditions in mice (Fig. 2 E), but some leukocytes are Ki67⁺ during EAE, suggesting local proliferation is also possible (Laaker et al., 2025). Microglia-like nerve-resident macrophages also exist inside nerve bundles, providing another line of innate defense (Smithson and Kawaja, 2010). The function of perineuronal myeloid cells in olfactory nerve maintenance is currently unknown and requires further study.

Peripheral blood-derived cells

Recruitment to the cpPME via the blood vasculature is supported using intravascular staining showing populations of blood-originating immune cells along olfactory nerve bundles and cpLVs during EAE (Laaker et al., 2025). Additionally, Fitzpatrick et al. showed that many of the dural blood vessels along the rostral-rhinal and basal olfactory hubs are fenestrated, a feature that allows immune cells positioned along the cpPME to sample from the peripheral blood and perhaps facilitate rapid recruitment of circulating cells (Zanluqui and McGavern, 2024; Fitzpatrick et al., 2024).

CNS-emigrating populations

Migration of immune cells from more distant brain and leptomeningeal spaces to the CP is also supported by rodent studies, which showed that after intracranial injection of fluorescent T cells (Goldmann et al., 2006) and monocytes (Kaminski et al., 2012), these cells were accumulated along olfactory nerve bundles. Additionally, migration of choroid plexus-originating CD11c⁺ cells from the CNS to the olfactory region via the rostral migratory stream is also supported, with CCR7-CCL19/21 and CXCR4-CXCL12 signaling pathways implicated as key mechanisms to facilitate trafficking of DCs to CP from the intracranial space (Clarkson et al., 2014; Clarkson et al., 2017; Mohammad et al., 2014; Hsu et al., 2019). Locally proliferated T and B cells from the rostral-rhinal confluence could also populate the cpPME via falcine veins (Zanluqui and McGavern, 2024; Fitzpatrick et al., 2024).

Skull bone marrow

Many of the immune cells in the perineural environment, as well as those bound to cpLVs, are CD11b⁺ and CD11c⁺ myeloid cells (Hsu et al., 2022; Laaker et al., 2025). Skull bone marrow can

contribute myeloid cells to the meningeal environments in a blood-independent manner via skull channels along the CSF-interfacing perivascular space of blood vessels (Cugurra et al., 2021). Work by our lab has characterized similar skull channel structures in mice linking perineural space of olfactory nerve bundles to a nearby pool of CP bone marrow (cpBM) in the ethmoid bone (Laaker et al., 2025). Perineural skull channels contained CSF1R⁺ immune cells during active neuroinflammation and the composition of cpBM skewed toward increased percentages of neutrophils and CD11c⁺ cells during EAE (Laaker et al., 2025), suggesting elevated myelopoiesis (Shi et al., 2022). Notably, these channels were connected to CSF-interfacing nerve bundles within and ventral to the CP, implicating local bone marrow in populating meningeal, foramina regions, and underlying lamina propria with immune cells near cpLVs (Laaker et al., 2025). Skull channels within the CP region complement recent findings of similarly described “nasal conduits” within rostral nasal bone marrow regions linking marrow to the underlying lamina propria (Gonzalez et al., 2024, Preprint). However, it is still unclear how much local bone marrow contributes to the cpPME niche and whether similar anatomical relationships exist in humans. In EAE, Cugurra et al. showed that monocytes infiltrating the CNS from adjacent skull and vertebral bone marrow exhibit a less inflammatory transcriptional profile compared with pro-inflammatory blood-derived monocytes (Cugurra et al., 2021). This suggests that cpBM, another direct CNS-adjacent niche, may similarly supply immune cells with a potentially less pathogenic phenotype, shaping local immune responses at the cpPME and influencing tolerance versus inflammation in neuroinflammatory diseases.

Olfactory submucosa

Immune cells that originate in the underlying olfactory submucosa have also been implicated to traffic into the CNS upstream perineurally, along olfactory nerve bundles (Dileepan et al., 2016; Asano et al., 2022). Asano and colleagues proposed that CCR2⁺ monocytes traffic along CCL2-expressing olfactory ensheathing cells into the CNS in a model of intranasal LPS exposure. In zebrafish, neutrophils can be seen trafficking into the CNS along olfactory nerves after damaging the olfactory epithelium (Palominos et al., 2022). Intranasally delivered cells, including regulatory CAR-T cells, have been suggested to traffic into the CNS through the CP (Chen et al., 2019; Fransson et al., 2012). With nasal immunity being highly intertwined with immune tolerance pathways (Miller et al., 2007; Metzler and Wraith, 1993; Wellford and Moseman, 2023) and the recent characterization of antigen presentation in lymphoid hubs within the dura (Fitzpatrick et al., 2024), a bidirectional immune cell trafficking route at the cpPME could be key to generate novel therapies for a variety of CNS diseases.

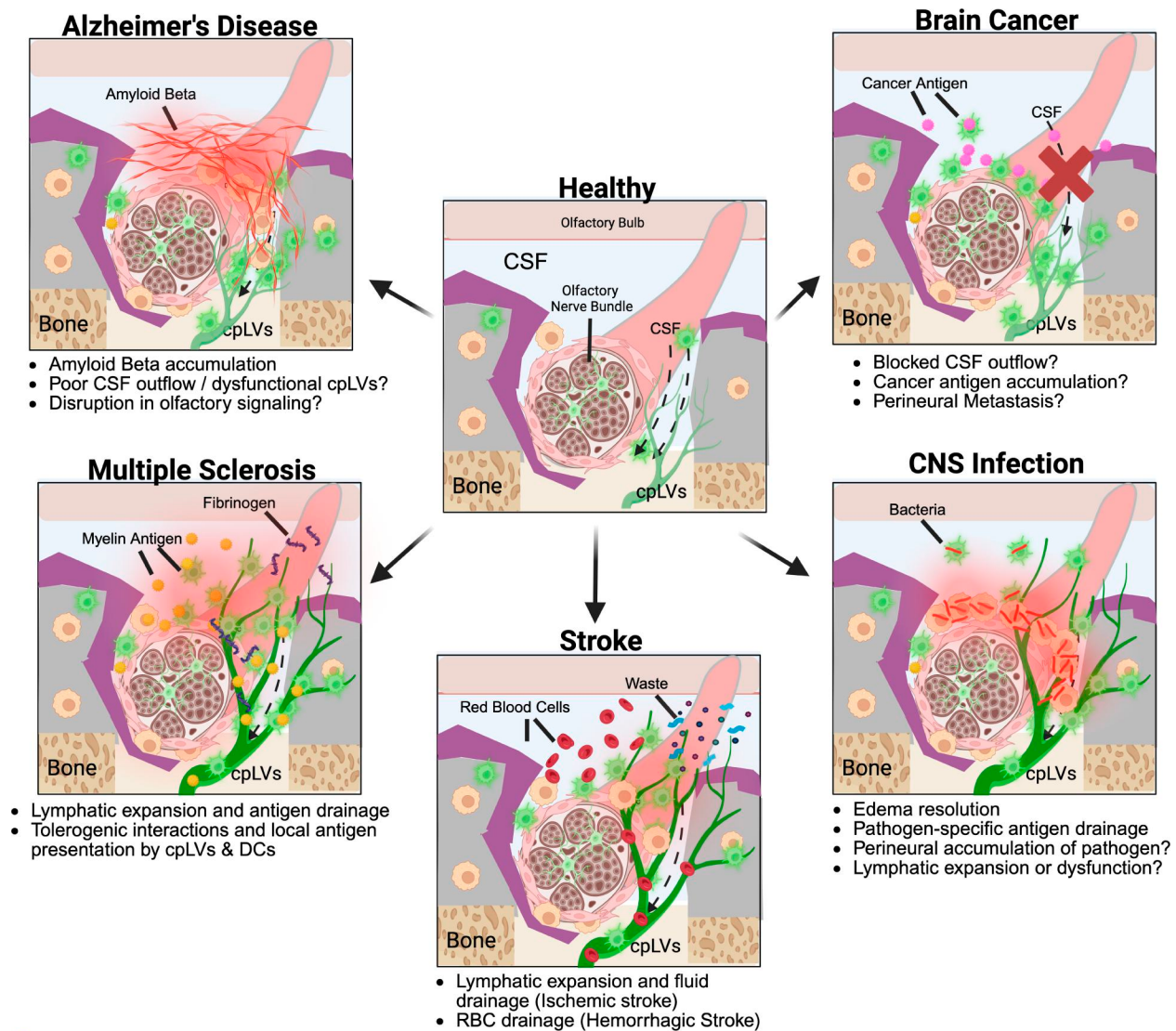
Relationship of CP to other CNS-immune hubs

As we saw in the previous section, the CP immune cells are likely recruited from different hub regions that include the nasal mucosa, skull bone marrow, DALT, and even from migratory

pathways linked to choroid plexus and rostral migratory stream deep within brain tissue. Furthermore, the CP is linked to other hub regions by CSF, ISF, vascular, and perivascular connections enabling this complex immune coordination. The existence of multiple, spatially distributed immune niches at CNS boundaries raises a fundamental question: why have the brain's borders evolved so many immune hubs? One simple explanation is specialization. Analogous to immune hubs in peripheral tissues, each CNS-associated hub may be tuned to specific microenvironmental cues and demands. For instance, the DALT situated above the olfactory bulb appears highly adapted to the underlying nasal environment, functioning as a pseudo-lymph node capable of sampling peripheral blood and intranasal antigens (Fitzpatrick et al., 2024). Although not yet fully characterized, it is plausible that adaptive immune responses initiated in the DALT establish an anticipatory layer of defense at the cpPME, which lies downstream and is vulnerable to intranasal pathogen invasion (Plakhov et al., 1995; St John et al., 2014; Goldin et al., 2025; van Riel et al., 2015; Audshasai et al., 2022; Guerlais et al., 2024; Dando et al., 2014). Other hubs, such as the skull bone marrow, choroid plexus, and leptomeninges, may serve similar roles by providing a rapid influx of innate immune cells, bridging the time period before adaptive responses from DALT and other regions are mounted. Ultimately, however, the cpPME is not only a potential site of pathogen entry but also plays a specialized role in facilitating CSF efflux and waste clearance. So these recruited immune cells from other hubs may be essential in helping remodel the cpPME, expanding lymphatics, clearing debris, in addition to maintaining health of the olfactory nerve bundle and preventing neuroinvasion. Importantly, olfaction is the most highly prioritized sensory modality in mice and is essential for their survival. Core olfactory behaviors including food seeking, predator avoidance, mate selection, and social interaction are all dependent on these intact olfactory nerve pathways. As a result, we hypothesize that immunity is similarly prioritized at the cpPME and integration with other hubs to ensure overall health of the organism.

Neuroinflammatory diseases and therapeutic targeting at the CP

As a site along the border between the CNS and the periphery, the CP provides unique opportunities to not only investigate neuropathologies but also to treat them. The blood-brain barrier protects the brain from potentially harmful compounds, but it has been a barrier limiting the delivery of therapeutically useful drugs, and posing a challenge for drug development. However, the CP represents a promising site, not only for its immunological relevance, but also for the ease of intranasal drug delivery, which is often non-invasive and more cost-effective (Craft et al., 2012; Correale et al., 2025; Kumar et al., 2018; Wellford and Moseman, 2023). In the following sections, we will investigate how the cpPME changes across different neuropathologies, and discuss its relevant biomarkers and potential interventions like intranasal drug delivery to target the cpPME across each disease (Fig. 4 and Table 1).



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Figure 4. cpPME in health and neuroinflammatory disease. Schematic illustrations depict how the cpPME, including cpLVs and olfactory nerve bundles, intersect with CSF drainage and immune interactions under pathological states. In the healthy (center) condition, CSF exits near olfactory nerve bundles and drains via cpLVs. In AD (top left), A β accumulates, potentially due to impaired CSF outflow and cpLV dysfunction, with possible effects on olfactory signaling. In MS (bottom left), fibrinogen deposition, lymphatic expansion, and myelin antigen drainage promote local antigen presentation by cpLVs and DCs, contributing to tolerogenic or inflammatory interactions. In stroke (bottom center), ischemic events drive lymphatic expansion and waste clearance, while hemorrhagic strokes facilitate red blood cell drainage. In brain cancer (top right), tumor-associated antigens may accumulate due to blocked CSF efflux, with possible perineural spread. In CNS infection (bottom right), pathogens can accumulate at CP, with cpLVs mediating pathogen-specific antigen drainage and edema resolution, and resulting in possible lymphatic expansion or dysfunction. Together, these models highlight the cpLV niche as a dynamic regulator of immune drainage across diverse neurological diseases.

MS

In MS, Th1/Th17 cells traffic into the CNS to promote demyelination (Murphy et al., 2010). The soluble efflux and cell-mediated transport of CNS antigens to the CLNs can drive the creation of myelin-specific T cells, exacerbating disease progression (Furtado et al., 2008; van Zwam et al., 2009b; van Zwam et al., 2009a). Experiments have shown that inhibiting meningeal lymphatic function prior to EAE induction can reduce CLN T cell activation and reduce EAE severity (Hsu et al., 2019; Louveau et al., 2018). However, not all antigen drainage from the CNS is pro-inflammatory, and outflow from the CNS, including

the CP, could also drive inhibitory signals depending on the phenotype of migratory DCs (Mohammad et al., 2014; Laaker et al., 2023). Some evidence suggests that in the context of EAE, DC migration and exposure to the olfactory system drive the creation of tolerogenic DC (tolDCs). In one study, inhibiting DC migration through the rostral migratory stream via intracranial injection of fingolimod resulted in spontaneous EAE in 2D2 mice (Mohammad et al., 2014). The study proposes that fingolimod treatment reduced tolDC egress to the CLNs, which exacerbated pathology (Mohammad et al., 2014). Similarly, our lab showed that lack of CCR7 (a key lymph node homing

Table 1. Potential therapeutic interventions at the cpPME

Disease	Pathophysiological issue at cpPME	Potential CP-targeted therapeutic intervention	Rationale/mechanism
MS	Pro-inflammatory myelin antigens via CP to cervical LNs drive autoreactive T cell priming Local cpPME immunosuppression is insufficient to produce tolDCs	TolDC delivery intranasally (to reeducate T cell responses) Intranasal tolDC promotion (IL-10, vitamin D) + increase tolDC egress across CP (VEGF-C)	Reducing antigen efflux could limit autoimmune priming; conversely promoting tolDC efflux can suppress disease Delivery at CP could skew immune responses toward tolerance and increase tolDC in CLNs
CNS infection (e.g., meningitis, encephalitis)	Inflammatory debris clearance; waste, fibrin, pathogens Fluid clearance and prevention of edema	Intranasal fibrinolytics (e.g., tPA) to clear CP obstruction; local antimicrobial delivery via nasal route Intranasal VEGF-C, CLN stimulation	Keeps CP drainage pathways open, maintaining CSF clearance; direct drug delivery bypasses BBB Immunomodulation at CP can reduce destructive inflammation while still allowing pathogen clearance and surveillance
AD	Impaired clearance of A β /tau? Poor CSF outflow $\rightarrow$ poor immune surveillance of CNS	Enhance CP lymphatic clearance (VEGF-C, intranasal lymphatic activators); intranasally (A β -degrading enzymes, neprilysin); CSF-to-nasal dialysis devices (experimental)	Restores A β /tau clearance into nasal mucosal lymphatics; intranasal delivery avoids BBB limits; device-assisted clearance could reduce toxic protein accumulation
Stroke (ischemic/hemorrhagic)	Stroke triggers release of CNS antigens and DAMPs into CSF; immune activation in cervical LNs can worsen systemic immunosuppression or autoimmunity Clot aggregation at CSF efflux points and increased need of edema clearance	Modulate cpLV drainage (VEGFR-3 blockade/MAZ51) temporary reduction of antigen efflux to LNs during the acute phase Fibrinolytics at CP (in hemorrhagic stroke) to prevent clot-mediated CSF blockage. Targeted VEGF-C delivery	Limiting antigen, DAMP, and cytokine efflux may reduce harmful peripheral inflammation responses after stroke Tolerogenic approaches could prevent poststroke inflammation; fibrin clearance maintains CSF outflow and prevents hydrocephalus
Brain cancer (e.g., glioblastoma)	Impaired CSF outflow (edema)? Impaired tumor antigen drainage through CP? Local cpPME immune suppression?	Enhance CP lymphatic drainage (VEGF-C). Nanoparticle antigen delivery via intranasal route Intranasal checkpoint modulators (e.g., PD-L1/PD-1 blockade locally at CP); + TGF- β blockade	Restores or boosts tumor antigen access to cervical LNs $\rightarrow$ stronger antitumor immunity; improves fluid homeostasis Local immune checkpoint control and TGF- β could prevent tumor-induced tolerogenic niche formation at cpPME, generating pro-inflammatory DCs

receptor) on intracerebrally-injected DCs exacerbated EAE, as these DCs were retained within the brain tissue and further restimulated myelin-specific T cells (Clarkson et al., 2017). Thus, it appears migration of DCs to CNS-associated drainage sites is important to control neuroinflammation potentially through removal of pro-inflammatory DCs and/or their conversion toward tolerance (Clarkson et al., 2017; Mohammad et al., 2014).

We hypothesize that cells and signals positioned along cpPME drainage pathways can work together to establish immunosuppressive niches in disease states such as autoimmune disease and cancer to drive creation of tolDCs. One exciting possibility is that nerve bundles themselves may coordinate this environment. In agreement with this, it has been shown that if peripheral nerve bundles become damaged or exposed to chronic inflammation, they trigger a tissue repair response resulting in the recruitment of anti-inflammatory macrophages into the perineural environments (Rotshenker, 2011; Baruch et al., 2025). Importantly, this perineural remodeling can trigger not only local immune suppression, but also suppression to the broader tissue environment (Baruch et al., 2025). In the context of MS, perineural spaces surrounding olfactory nerve bundles are rich with myelin-related antigens and perineural immune responses during EAE (Laaker et al., 2025; Hsu et al., 2022). Unlike myelinated nerve bundles such as the optic nerve, which are

common sites of neurodegeneration in MS/EAE (Xin et al., 2025), the unmyelinated olfactory nerve bundles might better support local suppressive niches during demyelinating diseases.

As mentioned previously, the lymphatics can also regulate immune cell populations and broader immune environments (Dieterich et al., 2017; Garnier et al., 2019; Santambrogio et al., 2019). Data from our lab support this immunoregulatory role, showing that cpLV environment upregulates immune cell adhesion molecules, antigen-presenting capabilities, and inhibitory molecules like PD-L1 in response to IFN- γ during EAE (Hsu et al., 2022). Thus, a suppressive cpPME niche likely counters Th1/Th17-driven pathology and may even help generate tolDCs, which drain to CLNs (Mohammad et al., 2014; Hsu et al., 2022). Therefore, IFN- γ modulation or PD-L1 agonists at the CP might enhance suppressive capabilities of cpPME and drive creation of tolDC without systemic effects.

Cancer

The CP is susceptible to damage and infiltration by cancers like olfactory neuroblastoma, schwannomas, and squamous cell carcinoma (Ghaffar and Salahuddin, 2005; Testa et al., 2024; Kim et al., 2015). Additionally, cancers in the brain and meninges can trigger hydrocephalus (Picart et al., 2021; Tamimi and Juweid, 2017) and release tumor antigens into the CSF. Thus,

cpLVs might promote fluid clearance and peripheral immune surveillance against CNS tumors. In agreement with this, studies that improved lymphatic drainage in the meninges enabled mice to mount a stronger immune response to glioblastoma tumors (Song et al., 2020; Hu et al., 2020). Typically, glioblastomas evade the immune system in part because of local immune suppression, but also through alterations in tumor antigen detection and reduced drainage from the CNS. For example, in mice, gliomas can shift CSF efflux away from the more dominant cranial drainage routes toward spinal lymphatic drainage routes instead (Ma et al., 2019a; Ma et al., 2019b). While the precise mechanism causing dysfunction at the CP outflow route is not fully resolved, the authors point to tumor-induced intracranial pressure and compression of perineural pathways as likely contributors to the impaired CSF circulation and reduced drainage into extracranial lymphatics (Ma et al., 2019b). Thus, it is possible that enhancement of lymphatic function through intranasal or intracisternal magna delivery of VEGF-C might restore outflow and improve tumor surveillance by DCs across this route (Song et al., 2020; Hu et al., 2020). With evidence that skull bone marrow and DALT mediate broad aspects of CNS immunity, investigations should interrogate how each CNS-immune hub including perineural foramina sites coordinates antitumor immune responses (Fitzpatrick et al., 2024; Dobersalske et al., 2024).

CNS infection

The CP lies directly above a pathogen-exposed olfactory mucosal layer, positioning the CNS to potential infections. Indeed, the CP is implicated as a site of neuroinvasion for a variety of pathogens via nerve bundles into the CNS (Plakhov et al., 1995; St John et al., 2014; Goldin et al., 2025; van Riel et al., 2015; Audshasai et al., 2022; Guerlais et al., 2024; Dando et al., 2014). Thus, the immune responses along the cpPME are not only important for coordinating drainage to the peripheral immune system, but can also help establish an immune environment, which ensures protection of the brain from infection (Wellford and Moseman, 2023). Asano and colleagues showed that intranasal LPS exposure was sufficient to trigger monocyte recruitment into the olfactory bulb, with highest levels accumulating along the olfactory nerve layer (Asano et al., 2022). Additionally, the recently characterized dural microenvironments, including the DALT above the olfactory bulb in the rostral-rhinal sinus of mice, sample intranasal viral antigens, present antigen, and generate adaptive immune cells locally (Fitzpatrick et al., 2024; Rebejac et al., 2022). Together, these findings support that neuroimmunity is highly attuned to the underlying nasal environment, coordinating anticipatory immune responses across the CP into the CNS. This aligns with recent evidence that intranasal vaccination routes confer region-specific protections to the nasal mucosal layer, which could be utilized to not only prevent systemic infections, but also better protect against neuroinvasion of specific pathogens through CP (Dando et al., 2014; Wellford and Moseman, 2023).

However, pathogens can still invade the brain causing CNS infection and meningitis, making coordination of the peripheral immune responses, fluid outflow, and waste clearance

immediate needs of the CNS. Our group has shown that when *Mycobacterium tuberculosis* (Mtb) bacteria are intracranially injected into the forebrain of mice, the bacteria accumulate not only in the dorsal dural regions near the injection site, but also at distant sites near several CSF-interfacing cranial nerve bundle regions including the olfactory nerves (Laaker et al., 2025). At the CP, intracranially injected Mtb bacteria aggregated within clusters of CD45⁺ immune cells around olfactory nerve bundles, within cpLVs, in cpBM, and in the nasal submucosa (Laaker et al., 2025). DCs are implicated to arrive to the CP from the subarachnoid space and the CNS, and they can be active traffickers of antigens or live pathogens in a predictable manner toward various CSF efflux sites along their migration gradients. In agreement with this, recent evidence suggests that trafficking of virus-infected macrophages might follow similar routes through the CP region in rhesus macaques (Alvarez et al., 2025). Thus, migratory DCs might not just play pivotal roles not only in initiating pathogen-specific immunity in lymphoid organs, but also in facilitating pathogen spread across their migration routes in the intracranial space, similar to peripheral organs (Harding et al., 2015). Leveraging understanding of immune cell migration pathways, and targeting pathogen cell carriers may prevent the spread of bacteria to drainage locations along the brain and meninges, but further investigation of the intracranial pathogenic spread is warranted. Importantly, patients with Mtb-induced meningitis will often experience cranial nerve dysfunction (nerve palsy) caused by debris or bacterial accumulation near cranial nerves and basal vasculature, which is often associated with lethal increases in intracranial pressure (Sharma et al., 2011; Wen et al., 2023).

Evidence also suggests that meningeal lymphatics are susceptible to pathogen-induced dysfunction, perhaps exacerbating hydrocephalus and poor pathogen control (Feng et al., 2024). While CNS infection has not been investigated at the CP region extensively, Kovacs and colleagues showed that brain *Toxoplasma gondii* infection impaired CSF drainage and could similarly alter antigen delivery to lymph nodes (Kovacs et al., 2022). However, their results also indicated that therapeutic enhancement of meningeal lymphatics through adeno-associated virus-mediated delivery of VEGF-C did not completely resolve the edema (Kovacs et al., 2024). In contrast, in a mouse model of cerebral malaria, a severe complication of *Plasmodium falciparum* infection, fluid drainage through the CP was efficient as edema developed (Haley et al., 2024). However, ligation of lymphatic vessels leading to CLNs impaired tracer clearance from the CP, worsened edema, and reduced survival after infection (Haley et al., 2024). Together, these results suggest therapeutic modulation of cpLVs in brain infection through lymphatic enhancement (Table 1) may play important disease-specific roles in edema resolution and peripheral immune responses against CNS-infiltrating pathogens.

Stroke

Strokes result in a sudden interruption of blood flow to an area of the brain leading to neuronal death. It is estimated that 78% of strokes in the United States are ischemic strokes (Lui et al., 2025), which occur after a thrombotic or embolic event

directly blocks blood flow resulting in ischemia. Hemorrhagic strokes occur after a blood vessel ruptures interrupting blood supply. In hemorrhagic stroke, the presence of the hemorrhage and inflammation results in cerebral edema. Interestingly, red blood cells in the CSF drain perineurally through cpLVs (Löwhagen et al., 1994; Madarasz et al., 2024). Lymphatic vessels around the CNS are important routes for responding to acute changes in ICP and waste clearance, and they have been explored as a potential therapeutic target for responding to cerebral edema in murine models of stroke. Boisserand and colleagues described that after transient middle cerebral artery occlusion (tMCAO), a mouse model of ischemic stroke, the prophylactic delivery of an adeno-associated virus expressing murine VEGF-C, a known driver of lymphangiogenesis (Antila et al., 2017) prior to tMCAO, minimized the area of infarct (Boisserand et al., 2024). At baseline, snRNA-seq analysis revealed that VEGF-C delivery altered expression patterns of *Sv2c*-expressing interneurons and inhibitory neurons to upregulate pathways associated with calcium regulation, G protein signaling, and brain neurotrophic factor pathways (Boisserand et al., 2024). Likewise, in another study intracerebroventricular pretreatment with AAV-mVEGF-C promoted dural lymphangiogenesis and improved motor recovery following tMCAO, although interestingly, it did not reduce infarct volume (Keuters et al., 2024). Evidence for the supportive role of meningeal lymphatic vessels (MLVs) in poststroke recovery also comes from studies, showing that MLV impairment leads to larger infarcts and slower neurological recovery (Yanev et al., 2020).

We recently expanded on these results by looking more specifically at cpLVs during tMCAO and utilized peripheral delivery of VEGF-C or MAZ51, a VEGFR-3 inhibitor, in the tMCAO model (Choi et al., 2025). This analysis demonstrated a robust lymphangiogenesis at the cpLVs starting at day 3, a peak at day 7, and regression by day 14 after tMCAO. Lymphangiogenesis was also seen in the deep CLNs (Choi et al., 2025). To understand the role of VEGF-C in the acute phase following stroke injury, VEGF-C156S was delivered through a microcatheter inserted in the common carotid artery and it was found that the infarct size was significantly increased without significant changes in cpLV area (Choi et al., 2025). Exploration of inhibiting VEGF-C signaling at days 0, 2, 4, and 6 after tMCAO through the administration of the VEGFR-3 tyrosine kinase inhibitor MAZ51 resulted in reduced lymphatic vessel diameter at the CP and MLVs, which importantly reduced brain infarct size (Choi et al., 2025). Similarly, Esposito et al. showed that intranasal MAZ51 1 day after tMCAO reduced stroke damage and dampened post-stroke immune response in lymph nodes (Esposito et al., 2019). Overall, the literature suggests that the timing of lymphatic vessel manipulation in stroke is integral to consider in therapeutic development as chronic, prophylactic lymphatic vessel stimulation by VEGF-C may help licensing and preparing lymphatic vessels to respond to an acute increase in intracranial pressure. However, during an acute insult, blocking VEGF-C signaling to dampen neuroinflammation and delayed lymphangiogenesis may be beneficial for brain recovery.

Neurodegenerative diseases

Decreased olfaction is one of the prodromal symptoms of neurodegenerative diseases such as Parkinson's disease and AD (Marin et al., 2018; Attems et al., 2015). Hyposmia, decreased sense of smell, and anosmia, loss of sense of smell, have been associated with increased mortality risk or disease progression in AD (Pinto et al., 2014; Ekström et al., 2017; Vassilaki et al., 2017), Parkinson's disease (Yoo et al., 2019; Doty, 2011), and Lewy body dementia (Mahlknecht et al., 2015). Therefore, there has been interest in utilizing olfactory function and nasal secretions as biomarkers for neurodegenerative diseases as it generally occurs in the prodromal phase of the disease and worsens with disease severity. Proposed theories for hyposmia include changes in neurotransmitter and neuromodulatory systems, reduction in CP foramina size with age, decrease in mucosal blood flow, and a reduction in mucosal metabolizing enzymes (Doty and Kamath, 2014; Attems et al., 2015). Nonetheless, we propose that deficits in olfaction should be investigated for dysregulation at the cpPME.

With disease progression in AD, there is decreased CSF efflux through the lateral ventricle system that is not due to a decrease in A β production (Spies et al., 2012; Wildsmith et al., 2013). De Leon et al. have demonstrated decreased CSF clearance utilizing intravenous ¹¹C-PIB and ¹⁸F-THK53 throughout the CSF efflux system: decreased efflux in the lateral ventricles (reduced by 23%) and severe reduction through the nasal turbinates (by 66%) (de Leon et al., 2017). Additionally, preprint research has suggested that human CP structure has decreased olfactory nerve foramina with AD progression (Zaragoza et al., 2021, Preprint; Kelly et al., 2024). Our group recently released a preprint demonstrating the importance of the cpPME including cpLVs in AD pathogenesis (Vrba et al., 2025, Preprint). We demonstrated that A β deposits at the cpLV regions and around olfactory nerve bundles in an aged APP/PS1 mouse model. The A β is associated with increased caspase-3 expression of the region, potentially resulting in LEC atrophy and cell death, leading to decreased CSF efflux measured through single-photon emission computed tomography and bead injections (Vrba et al., 2025, Preprint). In AD, there is increased CD45⁺ immune cell infiltration into the cpLV region. These results align with literature, which show that the dura and particularly the perivenous spaces are active areas of A β deposition, but there is still dispute of the overall contribution of meningeal lymphatics to AD pathology (Louveau et al., 2018; Antila et al., 2024; Plog et al., 2025). Further research is needed to characterize the immune cells that are recruited to amyloid deposits across the CSF-interfacing regions of the brain's borders (Plog et al., 2025), including near olfactory nerves (Vrba et al., 2025, Preprint). We argue that the cpPME may be similarly involved in other neurodegenerative conditions that have hyposmia as a prodromal symptom.

Within neurodegenerative conditions, there are a number of studies utilizing intranasal administration or modifying CSF efflux at the CP directly. There have been clinical trials (Craft et al., 2012) evaluating the safety and efficacy of intranasal insulin, which is thought to protect hippocampal synapses from A β oligomers through restoring insulin sensitivity (Freiherr et al., 2013). Rivastigmine, a cholinesterase inhibitor, delivered via an

intranasal spray is being evaluated, with the hopes of improving brain delivery and decreasing peripheral exposure (Guo et al., 2024). In preclinical models, a tau-specific antibody was delivered intranasally resulting in improved cognitive function measured through the novel object recognition and Y-maze tests, and reduced tau pathology in the brains of hTau mice (Gaikwad et al., 2024). Moreover, intranasal administration of a vaccine for A β has recently entered clinical trials (Frenkel et al., 2005, 2008; Lifshitz et al., 2012). Efforts are currently being made to directly modify CSF efflux through the creation of a brain drain at the CP in AD (Kelly et al., 2024). Additionally, there is recent interest that a surgical procedure to accelerate A β outflow to CLN via CLN-to-vein anastomosis, but findings are still controversial and awaiting additional experiments (Fang et al., 2025; Chen et al., 2025). Finally, photobiomodulation using combined transcranial and intranasal red to near-infrared light illumination has been indicated to confer neurological benefits in patients with neurodegenerative disease (Liebert et al., 2024; Saltmarche et al., 2017).

Concluding remarks and future directions

While studying basal skull foramina sites remains challenging due to its deep anatomical location, immune interactions occurring near foramina hold immense promise for discovery. Decalcified serial sectioning remains to be one of the quickest and highest resolution methodologies to observe specific skull foramina regions and the immune responses in different disease contexts. Other techniques such as tissue clearing and live imaging are also essential and should be expanded across disease states. One area of promise could be the utilization of 3D spatial transcriptional analysis with the ability to align serial sections of complex foramina regions (Khan et al., 2025). For regions that interface with multiple immune niches such as cranial nerve bundles, understanding how their internal and external immune environment changes as they traverse the skull is an exciting opportunity for discovery. Findings from the murine CP could then be compared and potentially extrapolated to other foramina regions of interest to understand how each site has unique susceptibilities and performs differential functions (Xin et al., 2025). Ultimately, more work is needed to identify how human CSF pathways communicate with nerves and lymphatics near cranial foramina regions during steady-state and diseased conditions. Additionally, researchers should also interrogate human ethmoid and nasal vascular studies and leverage biopsy samples from this region to define therapeutic targets and the immune profiles during brain disease. For CNS autoimmune diseases, can inhibitory pathways be maximized along the cpPME? Does the establishment of a tolerogenic environment along antigen drainage sites skew draining inflammatory migratory DCs toward tolerance? Can skewing progenitors in local bone marrow promote development of tolDCs specifically along these tissue niches? Can olfactory tests have clinical implications across neuroinflammatory diseases?

Finally, the CP is a physiological vulnerability during head trauma and a common site of entry for pathogens into the CNS. However, this unique vulnerability and permissiveness of the CP

region may also one day be exploited for biomarker detection and therapeutic delivery of novel brain-targeting drug treatments (Table 1). As research continues to illuminate the cpPME and other CNS-immune hubs, it is becoming clear that this region is not just a structural conduit but a dynamic hub of immune surveillance with broad implications for CNS health and disease. By uniting anatomical, immunological, and translational perspectives, future work at the CP may redefine how we understand and ultimately harness this unique CNS-immune hub.

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