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Brain borders at the central stage of neuroimmunology

Justin Rustenhoven[1,2,3,4,#], **Jonathan Kipnis**[1,2,#]

[1]Center for Brain immunology and Glia (BIG), Washington University in St. Louis, School of Medicine, St. Louis, MO, USA.

[2]Department of Pathology and Immunology, Washington University in St. Louis, School of Medicine, St. Louis, MO, USA.

[3]Department of Pharmacology and Clinical Pharmacology, the University of Auckland, Auckland, New Zealand.

[4]Center for Brain Research, University of Auckland, Auckland, New Zealand.

Abstract

The classical dogma suggested a disconnect between the immune and nervous systems, referred to as central nervous system immune privilege. However, recent studies have illuminated elegant workarounds at the borders of the central nervous system—putting these at the central stage of neuroimmune interactions. Despite the shared common goal to maintain homeostasis, under rare circumstances, immune and nervous systems may develop pathological interactions leading to neurological or psychiatric diseases. Here we discuss the recent findings that dissect the key anatomical, cellular, and molecular mechanisms that permit neuro-immune responses at the borders of the brain and spinal cord and the implications of these interactions for central nervous system diseases.

The immune and nervous systems display remarkable similarities for such diverse systems. While specially tailored to enable complex functions, both continuously survey our environment, relay cues, and adjust on demand to maintain homeostasis. Indeed, akin to the multidisciplinary nature of modern science, these systems communicate—both within and between themselves—in a multilingual manner. The classical example of immunological communication is through cytokine secretion from one cell, which acts in a paracrine nature on another cell to dictate its function and orchestrate a specific response. Similarly, in the brain, neurotransmitter release from pre-synaptic terminals will act on corresponding receptors or ligand-binding domains in the post-synaptic density of another neuron to enhance or repress their firing. Interestingly, neurons of the central nervous system (CNS) and peripheral nervous system also express cytokine receptors permitting diverse

[#]Corresponding authors. rustenhoven@wustl.edu or kipnis@wustl.edu.

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J.R. and J.K. discussed the content of the manuscript including the selection of key studies, wrote and edited the manuscript, and generated figure outlines.

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responses to immune cell-derived cytokines[1–3]. Conversely, immune cells express receptors for neurotransmitters and neuropeptides—signaling molecules derived from neurons— and immune responses can be modified by neuronal signaling[4,5]. These data are increasingly evolving with recent observations that neurons themselves can also express cytokines, such as interleukin 13 (IL-13), at pre-synaptic vesicles and corresponding cytokine receptors at the post-synaptic density, suggesting a form of neuronal communication based on "immunological molecules", yet devoid of actual immune cells[6]. Neurons can also adopt communication strategies utilized by the immune system to regulate neuronal connectivity, including the expression of major histocompatibility complex (MHCI) and complement proteins C1q and C3b, that enable direct neuronal pruning[7] or synapse elimination via microglial engulfment[8]. Similarly, immune cells—such as B cells—can produce the neurotransmitter gamma-aminobutyric acid (GABA) and this can promote the differentiation of anti-inflammatory macrophages, highlighting an immune-immune interaction through classically neuronal-derived signals[9]. Collectively, diverse interactions underlie the complex communication between nervous and immune systems (Figure 1).

CNS control by immune contributions

The classical sensory and motor construction of the brain is viewed as a homunculus, whereby particular regions of the primary motor and sensory cortices control movements and sensation in a particular body region. In a similar manner, neuronal populations in the brain display anatomical or cellular heterogeneity in cytokine receptor patterning, permitting site-specific responses to immune-derived stimuli. Neuronal populations display both region-specific and subtype-selective cytokine receptor expression, as can be seen for IL-17Ra[2,3,10], IL4-Ra[1], IL-13ra[6] and likely additional, yet unexplored, cytokine receptors. This cytokine receptor heterogeneity may contribute to shaping distinct CNS functions, and can be viewed as a form of neuromodulation[11]. Thus, much like its motor and sensory orchestration, the brain appears to display an immunological homunculus. Reciprocal observations have also been made, whereby many tissues display distinct innervation patterning by peripheral nerves. In particular, recent works have demonstrated the role of sympathetic innervation of secondary lymphoid organs, including the spleen and lymph nodes— and the importance of sensory inputs in shaping lymphoid functions in these tissues[12,13].

The brain is a master regulator of the body, and thus it is critical it understands the state of the periphery. Indeed, it does, and this can be seen in neuronal responses to peripherally-derived cytokines, and the generation of behavioral responses, for example sickness behavior that limits pathogen spread between individuals[14]. The brain may even store memories of past peripheral inflammatory insults, exemplified in experimental colitis and peritonitis models, where they are presumably encoded in highly localized neuronal ensembles, within distinct anatomical regions[15]. While these responses were localized in the insular cortex, it is plausible that different regions of the brain may encode memories for diverse immune responses. Neuroimmune interactions can also occur through specialized anatomical locations. The circumventricular organs surrounding the third and fourth ventricles contain highly permeable capillaries and specialized endocrine neurons, enabling continuous communication with blood-derived signals[16].

More recent observations have uncovered additional and unexpected forms of neuro-immune crosstalk occurring at the border tissues of the brain. Beyond the importance of the brain in recognizing peripheral immune responses, it is equally important for the immune system to see what is going on in the brain—yet this fundamental feature of CNS immune surveillance was historically viewed as absent, or at least limited, in this organ.

CNS immune privilege

The concept of CNS immune privilege has been extensively reviewed, debated, and reinterpreted in recent years[17–21]. The original definition stemmed from classical transplantation experiments, and was interpreted as an evolutionary drive to protect delicate tissues, incapable of self-renewal, from damage elicited by a complex immune response[17–21]. In a series of seminal studies, researchers transplanted autologous tissue, or sarcomas, into different tissue compartments and assessed their ability to survive in distinct sites. In general, while transplantations into peripheral tissues such as the skin were rapidly rejected, transplants into the brain parenchyma were found to survive[22,23]. The rejection occurs primarily through an adaptive immune response. First, antigens—that is immunogenic matter arising from the transplant—should drain to lymph nodes as free antigen or be taken up by tissue resident antigen presenting cells (APCs) and migrate to draining drain lymph node via a lymphatic network. APCs capture these antigens and present them on MHC molecules. The antigen-MHC complexes are then recognized by T cells, and along with co-stimulatory molecules and instructive cytokines, results in T cell priming. These activated T cells obtain a specialized phenotype, consisting of integrin expression allowing them to bind to tissue endothelium, and chemokine receptors to enable tissue homing. Upon entering the antigenic site, a T cell can be reactivated by local presentation of antigens by tissue resident APCs, resulting in robust cytokine secretion that can directly target the pathogen or malignancy, as well as orchestrating local phagocytes or other stromal cells to facilitate its removal and promote the healing of the tissue. Interestingly, the CNS was believed to lack several fundamental features of this axis that would appear to explain why foreign matter was poorly rejected, giving rise to the concept of CNS “immune privilege”.

Specifically, this concept was perpetuated by the presence of distinct anatomical features of the CNS, namely 1) the blood-brain barrier (BBB)—a unique CNS vasculature displaying high expression of cellular tight junctions and drug-efflux transporters, and low-levels of leukocyte adhesion molecules and transcytosis, 2) the lack of lymphatic vasculature—a vascular network that drains antigens or APCs and permits immunosurveillance of tissue perturbations at draining lymph nodes and 3) the inability of microglia—the resident macrophages of the CNS—to efficiently present antigens and the relative lack of specialized APCs in the brain parenchyma. In recent years, remarkable workarounds for each of these caveats has been described to enable immune surveillance of CNS tissues, largely situated in the borders of the brain.

An updated understanding of CNS-immune interactions

In hindsight, these early studies illuminated the lack of absolute immune privilege as we now understand it—more than 100 years prior. One particularly critical (yet perhaps overlooked) observation was that immune rejection of xenografts was elevated when transplants were performed closer to the cerebral ventricles—the site of active cerebrospinal fluid (CSF) production[22]. These findings suggested that antigen recognition of this fluid that bathes the brain and spinal cord could be a critical factor in immune surveillance. In the late 1900s, CNS-immune connections were expanded with seminal observations that activated T cells can enter the CNS, and that CSF was observed to drain into cervical lymph nodes[24–26]. Later still, an improved understanding of CSF and brain interstitial fluid mixing through intramural peri-arterial drainage and/or glymphatic pathways and clearance via CNS-draining lymphatics would explain these observations[27–31]. These mechanisms enable the removal of brain waste into the CSF where it can be subsequently drained by the lymphatic system situated at the brain borders to CNS-draining lymph nodes, permitting immune surveillance of brain antigens[27–31]. Indeed, it was recently demonstrated that augmentation of this axis, via enhancing meningeal lymphatic drainage of tumor antigens, facilitates the immunological rejection to CNS tumors[29,32].

It is increasingly apparent that rather than the CNS tissues displaying immune privilege, these have unique immunological orchestrations reflecting the complexity of the tissue they protect[33]. In particular, recent observations have illuminated the importance of the brain borders; the meninges, choroid plexus, CNS-draining lymph nodes, perivascular spaces, and the skull and vertebral bone marrow, in permitting immune surveillance (Figure 2). Here, various aspects of the immune system can sample CNS antigens[34–37], shape B cell tolerance[38], protect the brain from pathogenic insults[39], manipulate behavioral paradigms[1,2,10,40,41], and provide bespoke immune cells to the brain itself during health and diverse insults[42–44].

Neuroimmune contributions in the meninges

The meninges are a triple-layered membranous structure that ensheath the brain and spinal cord (Figure 2). These three layers include the pia mater that contacts the brain surface, the dura mater that contacts the cranium and vertebra, and the arachnoid mater underneath the dura mater, creating a subarachnoid space between arachnoid and the pia, through which CSF flows. Initially described as a protective sac to cover the brain, the meninges are now recognized as an active participant in diverse brain functions. Meningeal-derived cues in the form of secreted cytokines, chemokines, and growth factors contribute to brain development[45], neuronal firing[2], neuronal connectivity[41], and homeostatic rodent behaviors[46]. Additionally, the meninges have several unique features that enable immunological cross talk with the brain parenchyma (Figure 3).

Immunological landscape of the meninges

High dimensionality techniques including spectral flow cytometry, mass cytometry, and singlecell RNA-sequencing (scRNA-seq) have provided a deep characterization of meningeal immunity and the construction of richly informative tissue atlases[2,34,47–49].

Unlike the brain parenchyma—whose immune cell diversity is restricted almost solely to microglia—the meningeal layers represent complex immunological hubs containing myeloid and lymphoid populations including monocytes (Ly6c^{hi} and Lyc6^{lo}), neutrophils, dendritic cells (cDC1s, cDC2s, pDCs, migDCs,), B cells (immature and mature), plasma cells, T cells (CD4, CD8, and γδ T cells), Natural Killer (NK) cells, NKT cells, mast cells, eosinophils, type 2 innate lymphoid cells (ILC2s), and macrophages[2,34,47–50]. Proportionally, these populations change across the distinct meningeal layers and the relative diversity of immune cells is highest in the dura when compared to leptomeningeal layers[48]. While not strictly in the meningeal tissues, immune cells are also present—albeit in low numbers—in the CSF that flows within the subarachnoid space, and display substantial enrichment of CD4 and CD8 T cells[51,52]. Importantly the meningeal immune cells are not evenly tiled throughout the border tissues but localized to discrete regions that permit their tissue-specific functions. In the dura, many immune cells, including macrophages, αβ and γδ T cells, B cells, plasma cells, and ILCs display clustering around the dural sinuses, likely as a consequence of a supportive stromal niche[2,34,43,53]. Tiling of populations in leptomeningeal layers is less clear, but macrophages are both distributed throughout the subarachnoid space and situated around large vessels situated within these tissues[54,55].

Meningeal cytokines and their brain targets

Cytokine signaling on discrete neuronal populations alters neuronal physiology and function[1–3,10,40,41]. Through this neuromodulation of distinct brain regions, the immune system is able to shape the behavior of mammals[1–3,10,40,41]. Some signals—likely from tonic homeostatic signaling—maintain physiological behavior. IFNγ alters sociability[41], IL-17 maintains anxiety and spatial learning[2,40], and IL-4 regulates learning and memory[1,56]. Other cytokines such as IL-1β can also act on discrete neural cells to maintain sickness and avoidance behaviors, likely an evolutionary drive to prevent pathogen dissemination between individuals[57]. Importantly, the brain is largely devoid of cells that produce these cytokines, yet the brain borders possess these in abundance[48]. The meninges contain numerous innate and adaptive populations capable of producing diverse cytokines, including IFNγ, IL-17, IL-4, and IL-1β[1,2,14,34,41,48]. Manipulation of meningeal cytokine producing cells, for example depletion of γδ T cells or of their derived IL-17 was sufficient to phenocopy the effect of global cytokine depletion, suggesting the meninges are a critical source of these immune cues[2,40]. For others cytokines a direct meningeal to neuronal signaling is posited, yet not completely confirmed[1,56].

Meningeal vasculature allows immune trafficking

The CNS contains specialized vasculature that largely limits homeostatic immune trafficking. This is achieved by high expression of the tight junctions claudin-5 (Cldn5) and occludin, as well as a low level of leukocyte adhesion molecules, including intercellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM1), that enable binding to integrins expressed on leukocytes, including lymphocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) respectively[58]. This restrictive vasculature was fundamental in the perception of the brain as an immune privileged site. In contrast, the meninges contain specialized vasculature primed for immune surveillance. In particular, the sinuses embedded in the dura mater—large venous structures that

drain blood from cerebral veins—express high levels of adhesion molecules and low levels of tight junctions, that facilitates immune trafficking[34]. Further, the dural sinus niche contains endothelial, stromal, and immune populations that express homeostatic chemokines, including CXCL12 and CXCL16, to promote chemotactic recruitment of diverse lymphoid and myeloid populations[34,42]. Moreover, the sinus-adjacent stromal tissue, comprised of abundant extracellular matrix and additional ligands, represents a niche for tissue-resident memory T cell retention following extravasation[34]. The leptomeningeal vasculature may also enable immune cell trafficking, via upregulation of VCAM1 and ICAM that enables VLA4 or LFA1 engagement, and through leptomeningeal macrophage production of CCL5, and CXCL9–11 that promote chemotactic recruitment[55]. However, such trafficking through the leptomeningeal vasculature is largely limited to inflammatory conditions, or by autoreactive CNS T cells, as these vessels phenocopy the CNS vasculature to restrict access of cells and blood-derived components to the CSF[54,55]. Importantly, under inflammatory conditions, all vascular beds, including brain, leptomeninges, and dura upregulate adhesion molecules and allow robust trafficking[25,34,54,55,59,60]. One intriguing question that remains is the exact contributions of these different routes for cells that enter the CNS during insults or under homeostasis.

Meningeal immune cells present CNS antigens

Sampling the antigenic content of a tissue is critical to the recognition of perturbations, be this pathogens, tumor neoantigens, or self-antigens exposed after tissue injury. Via brain ISF and CSF mixing through the glymphatic or intramural peri-arterial drainage systems, CNS waste is continually flushed into the CSF and this fluid forms a soluble sink, mirroring the functional state of the brain[27]. Despite the presence of an arachnoid layer, commonly touted as a dural-arachnoid barrier, the CSF is constantly exposed to the dura mater. Via yet undefined routes, but potentially via perivascular pathways along cerebral veins that traverse the arachnoid mater, CSF constantly effluxes to the dura mater, largely restricted to sites surrounding the dural sinuses[34,61,62]. These observations have been confirmed in rodent models using live imaging of fluorescent tracers, human studies using gadolinium based magnetic resonance imaging (MRI), or human mass spectrometry analysis demonstrating the presence of CNS-enriched antigens in the parasagittal dura[34,61,62]. Antigens delivered to the CNS or CSF are captured and processed by dural APCs, including dendritic cells, macrophages, and B cell, and can present these to patrolling T cells, allowing immune surveilance[34,54]. In experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis induced by peripheral immunization of myelin oligodendrocyte glycoprotein (MOG), T cells accumulate within the dura mater and the leptomeninges, likely as a result of local presentation of myelin antigens[34,54]. Thus, the dura mater, with coordinated immune hubs around the dural sinuses, as well as the underlying leptomeninges, can sample the antigenic content of the brain, and present this to circulating peripheral T cells to enable the recognition of CNS dysfunction, and can mount a functional response. While the dura permits homeostatic immune surveillance, once pathological interactions occur, the inflammation proceeds to and predominates at the leptomeninges and the brain parenchyma[54,55].

Meningeal CNS antigen sensing shapes B cell tolerance.

The meninges are constantly bathed in antigenic matter arising from the CNS. This enables another fundamental feature of the adaptive immune response, elimination of autoreactive B cells. The dura mater contains a large proportion of mature B cells under steady state conditons[2,34,38,42,43,47,48,63]. Recent works have also demonstrated that this tissue contains developing B cells—including pro-, pre- and immature B cells—a function previously believed to be restricted to the bone marrow[38,43,63]. This lymphopoietic feature is likely a result of a supportive stromal niche around the dural sinuses containing developmental ligands including CXCL12 and IL-7[34,38,43]. During development in the bone marrow, immature self-reactive B cells exposed to self-antigens undergo elimination via central tolerance to avoid autoimmunity. Intriguingly, B cells that recognize MOG—a component of CNS myelin that is largely restricted to the brain—were eliminated specifically in the dura mater, but not peripheral bone marrow, demonstrating an additional site for immune tolerance[38]. These data demonstrate that exposure of CNS antigens to the dura mater is critical in shaping the B cell receptor (BCR) repertoire in cells situated at the CNS borders.

Upon T cell stimulation, B cells may undergo additional maturation to become antibody-producing plasma cells, primarily of the IgA producing phenotype, a dimeric antibody form most commonly associated with mucosal surfaces and which provides first-line protection against pathogenic infections[34,39]. Shared BCR tracing suggested that these dural IgA-producing plasma cells are educated in the gut, and later transit to the meninges where they reside around the dural sinuses[39]. Critically, these cells protect the brain from blood-derived pathogens and upon pharmacological or genetic deletion, blood-derived pathogens could more readily infect the CNS[39]. Thus, local entrapment of pathogens at these brain borders are critical in preventing CNS infections.

Meninges contain a lymphatic network.

The belief that the CNS lacks a lymphatic network was an often-touted statement underlying the mechanism of so-called ‘immune privilege’. However a lymphatic network exists in the dura mater, is evolutionary conserved[64–67] and is capable of draining the CNS via the CSF. This lymphatic network develops postnatally, and is restricted largely along the dural sinuses[68]. As an unlikely coincidence, lymphatics are positioned in regions where CSF can access the dura mater, permitting access to CNS-derived waste[34,61]. This sinus-specific location is maintained by VEGF-C producing smooth muscle cells that are highly enriched around the sinuses[34,68]. Unlike lymphatic networks in other peripheral tissues, disruption of the lymphatic mitogen VEGF-C or its corresponding receptor VEGFR3 enables rapid regression, suggesting this is a delicate network, prone to dysfunction[68,69]. While controversies persist on the exact contribution of different lymphatic routes to CSF drainage, numerous groups have demonstrated that meningeal lymphatics have access to and subsequently drain this fluid[34,64,65,69–72]. Ablation of this network was sufficient to impair drainage to deep cervical lymph nodes[70,71] while, augmentation of this meningeal lymphatic network via VEGF-C delivery was sufficient to restore impaired drainage in aging[70,71].

The meningeal lymphatics exist as a continuous network encompassing the dorsal and basal aspects of the brain borders largely following the venous sinuses in the dura mater and

terminating in the draining deep cervical lymph nodes[65,68,69,73]. The majority of lymphatic mapping has been performed in rodent studies, identifying a network of initial lymphatic capillaries largely in the lateral regions of the transverse and sigmoid sinuses, surrounding the rostral rhinal vein and in the cavernous sinuses, enabling CSF uptake[28,68,69,73]. These initial lymphatic structures transition into collecting lymphatic networks as they progress towards the draining lymph nodes and 3D imaging of these structures using tissue clearing protocols and light-sheet microscopy revealed the complete anatomical basis for these connections[73]. Recent advances in mapping meningeal lymphatics in humans using contrast-enhanced MRI have largely confirmed these observations, demonstrating both CSF efflux to perisinus locations in the dorsal and basal aspects of the dura, as well as previously unknown locations surrounding the cavernous sinuses, and uptake at these locations into the dural lymphatic network[61,62,64,73]. Critically, this lymphatic network in the CNS borders enables the antigenic content of the brain access to draining lymph nodes facilitating immune surveillance of the CNS.

Brain border macrophages promote leukocyte recruitment and control CSF dynamics

In addition to the diverse immune populations that survey the brain borders, resident macrophages are present in the leptomeninges and perivascular spaces[47,48]. Elegant fate mapping studies using Mrc1^{CreERT2} and Lyve1^{CreERT2}-based reporter mice recently demonstrated that like microglia, meningeal macrophages are long-lived and originate from a common prenatal progenitor in the yolk sac[74]. In contrast, perivascular macrophages are derived from perinatal meningeal macrophages after birth in an arterial smooth muscle cell and integrin-dependent manner[74]. The phenotype of CNS macrophages is therefore defined by their anatomical locations and adopted niche. These meningeal and perivascular macrophages are situated at the interface between the brain parenchyma and peripheral blood and function as first-responders in diverse neuroimmune interactions.

Meningeal macrophages are critical for facilitating immune cell trafficking, retention, and activation during neuroinflammatory diseases. Following EAE induction, these cells upregulate integrins that bind VLA4 and LFA1 expressed on activated T cells and promote their attachment within the leptomeningeal spaces[55]. By doing so, they enable retention of activated T cells within the CSF-filled spaces. Further, meningeal macrophages can produce diverse chemokines, including CXCL9–11 that recruit activated T cells to leptomeningeal sites in inflammatory states[55]. As a result of their location within the subarachnoid space, these macrophages are continuously bathed in CSF and are therefore efficient at capturing and presenting endogenous CNS-derived antigens present in the CSF[54].

Recently, we demonstrated an unexpected role for perivascular macrophages in controlling CSF dynamics under homeostasis[50]. Depletion of perivascular and leptomeningeal macrophages (collectively referred to as parenchymal border macrophages, or PBMs) using clodronate containing liposomes or genetic tools resulted in impaired arterial pulsation, which is a driving force for CSF influx from periarterial spaces. Ultimately, this resulted in impaired CSF and brain ISF exchange and in impaired removal of CNS waste[50].

Choroid plexus and neuroimmune interactions

The choroid plexus is situated within the ventricles of the brain outside the pia matter at the CNS borders (Figure 2). It consists of modified secretory epithelial cells, linked by tight junctions, that surround a network of highly permeable capillaries and a loose connective stromal network. The choroid plexus is primarily responsible for CSF production that results from the filtering of blood from the fenestrated endothelial network and secretion into the cerebral ventricles via specialized epithelial secretory cells[75]. Following CSF secretion, ciliated ependymal cells that line the ventricles facilitate movement of CSF outwards from the ventricles to the subarachnoid space.

scRNA-sequencing and mass-cytometry analysis of the choroid plexus revealed the presence of numerous innate and adaptive immune populations[48,76]. The transcriptomic profile of choroid plexus immune cells—particularly macrophages—was varied across age and in different ventricles, suggesting partial heterogeneity in these niches[76]. Of particular note, Lyve1$^+$ macrophages predominantly exist in CSF-facing spaces, yet CD74$^+$ macrophages (an MHCII-associated gene) were largely restricted to the stromal compartment[76].

As a deep-lying brain structure, live-imaging of choroid plexus immune trafficking is complicated. Recent advances using intravital imaging of brain-implanted lenses has permitted the imaging of these deep compartments. This approach revealed patterns of macrophage movement that were dependent on whether they sit in the blood-facing stromal compartment or CSF-facing epiplexus sites[76,77]. Macrophage cell bodies within the stromal space were largely immobile but displayed movement of processes, much like microglia, while those in the epiplexus displayed substantial cell body motility[77]. Stromal macrophages also rapidly accumulate blood-delivered tracers that extravasated into the stromal space, suggesting a protective function to limit access of unwanted matter to CSF[77].

Like the dura mater, the choroid plexus endothelium is fenestrated, displays low levels of tight junctions, and abundant adhesion molecule expression[76]. Short-lived cells such as neutrophils and monocytes are present in the choroid plexus, suggesting continuous homeostatic trafficking from the permissive blood vessels and diverse chemokines are present under steady-state that could recruit myeloid populations[48,76]. Whether abundant T and B cell trafficking occurs under homeostasis remains to be confirmed, but choroid plexus T cells display a high expression of CXCR6, consistent with a tissue resident memory phenotype[48,76].

Trafficking across the permeable choroid plexus vasculature allows access to the stromal space, yet a layer of specialized epithelium separates this compartment from the CSF. Trafficking across the choroid plexus epithelium into the CSF may occur during inflammatory states[78]. While elevations in choroid plexus immune cells are present after spinal cord injury or following peripheral LPS administration, whether these cells cross the epithelial barrier remains unclear[78,79]. Recent advantages in *in vivo* imaging will likely provide critical insight into immune cell trafficking at this region[77].

Lymphatic drainage routes at the brain borders

The classical dogma of CSF drainage described its direct passage into the dural sinuses via arachnoid granulations[80]. Such a route would remove CSF with its CNS-derived antigenic mater directly into blood, rather than lymph, negating any potential for immunological surveillance of this fluid. Several recent observations have begun to describe alternative CSF drainage pathways[65,66,69,81] and indeed fluorescent tracers injected into CSF appear in lymphatic circulation before their appearance in the blood[81]. As aforementioned, the brain borders are exposed to CNS antigens via constant access to the CSF and may serve as a "sink" for the drainage of CSF. Distinct routes for drainage of this fluid have been described, including drainage via the cribriform plate and along cranial nerves[81–84], and drainage via the meningeal lymphatics[69,28,64,66,70,72] (Figure 2).

Recent advances in whole organ mapping using 3D tissue clearing and imaging procedures revealed an interconnected network of the meningeal lymphatics in the dorsal and basal aspects of the skull and the cavernous sinuses, that passed through the foramina and fissures of the skull to access the draining lymph nodes[73]. This network remained distinct from the lymphatic network in the cribriform plate of the nasal cavity, suggesting these sites represent two divergent anatomical networks that may function to drain different CSF compartments[73]. The relevance of each respective route remains unclear, but it appears that each pathway has a role, though this could be different depending in physiological or pathological states. Nevertheless, numerous lymphatic networks in the brain borders have access to CSF, and thereby matter arising from the CNS.

Despite different anatomical routes, the aforementioned studies agree that lymphatics drain CSF to deep (and to a lesser extent superficial) cervical lymph nodes. This has been confirmed using extensive rodent imaging modalities including post-mortem analyses of CSF-delivered fluorescent tracers or bone-marrow-derived dendritic cells[28,68,70,71,73,85], live stereomicroscopy of dextran beads and fluorescent tracers[65,70], and MRI of CSF-delivered contrast agents[69,82]. Exactly which lymph node(s) CSF drains to in humans remains unclear. However, molecular tracers used as a surrogate for CSF movement can be observed in the lymphatics at the brain borders of humans[64,73] and cervical lymph nodes of human patients demonstrate the presence of the CNS-enriched myelin protein MOG[86]. An unresolved question is exactly how much CSF drains through these different routes. While this may be critical in understanding their contribution for bulk drainage of CSF waste, for example amyloid beta removal, it is comparably less important for immunosurveillance purposes, where even a small fraction of CSF drainage enables the surveillance of CNS antigens in lymphoid organs.

Skull bone marrow as a private reservoir for CNS immunity

Along with structural support, bones harbor marrow where hematopoiesis—the formation of new blood cells—occurs. The bone marrow in the skull and vertebrae surrounding the brain and the spinal cord harbor hematopoietic stem cells and supportive stromal niches, enabling the formation of lymphoid and myeloid immune cell lineages. Typically, newly formed leukocytes within the bone marrow will lose bone-marrow retention cues enabling

entrance into the peripheral blood circulation. However, the skull and vertebral bone marrow possess distinct anatomical structures that permit direct bi-directional passage between these sites and the brain border tissues (Figure 4).

Skull bone marrow and meningeal channels

Remarkably, the skull and vertebrae bone marrow have direct conduits that permit migration of immune cells to the CNS borders, independent of a blood route[42–44,87,88]. These pathways are formed by ossified “channels” that surround vascular projections between the CNS tissues and bone marrow[42–44,87,88]. These channels originate within the marrow itself, traverse the bone cortex, and terminate within the dural mater[42]. While these channels are not unique to skull and vertebrae bone marrow and have been observed connecting the tibial bone marrow to surrounding tissues[44], the uniqueness of these bone marrow sites lies in the fact that they have specific access to the CNS borders[38,42–44].

Utilizing parabiosis, skull transplantations, and selective irradiation paradigms with bone marrow transplants, the skull and vertebral bone marrow was found to directly provide leukocytes to the homeostatic dura mater, without requiring trafficking via blood[38,42,43]. Cells could be observed crawling through the channels surrounding bridging vessels[38,42,43]. This intriguing pathway provides direct access of skull and vertebrae myeloid cells to brain borders tissues, including short-lived monocytes and neutrophils, and longer-lived dendritic cells and macrophages[42]. Further, these channels enable direct migration of B cells as well as pro-, pre- and immature B cell progenitors to the dura, where they undergo extramedullary maturation, outside of the bone marrow[38,43]. It should be noted that an alternative technique using skull bone marrow leukocyte labelling failed to observe this[43,52].

Understanding the cues that recruit immune cells from CNS-associated bone marrow will be critical in identifying mechanisms to manipulate this trafficking route. The homeostatic dura expresses several chemokines for immune cell recruitment including CXCL12, CCL1, and CCL2[34,38,42,43]. However, it is unknown whether these cells use classical integrins such as LFA1 and VLA4 to crawl abluminally within these channels. For leukemia cells, α6 integrin-laminin interactions were found to permit cell infiltration from the skull bone marrow to underlying tissues, suggesting extracellular matrix components could facilitate abluminal trafficking[87]. It would be particularly interesting to define whether specific cues could be identified to recruit cells from bone marrow versus blood—which would enable methods to selectively manipulate trafficking into brain border tissues from distinct origins.

Skull and vertebral bone marrow channels supply immune cells to CNS tissue under pathologies

While skull and vertebrae channels contribute to the meningeal immune diversity under steady state conditions, they also facilitate leukocyte trafficking during CNS insults. Remarkably, immune cell migration is no longer limited to the brain borders in pathological contexts, and the skull and vertebrae bone marrow-derived cells can access the parenchyma of the brain and spinal cord[42,44]. Under homeostasis, relatively few skull or vertebral bone-marrow derived cells were found to traverse the arachnoid layer, yet after diverse CNS injuries, this does not hold true. These observations suggest the arachnoid barrier functions

as a checkpoint for homeostatic skull or vertebral bone marrow migration that is overcome in pathological contexts.

Using a murine middle cerebral artery occlusion stroke model, skull bone marrow-derived neutrophils were found to preferentially migrate into the brain parenchyma compared to their peripheral counterparts, via direct migration through skull bone marrow channels[44]. Similar results were observed in other models of CNS diseases, including spinal cord injury, EAE, and optic nerve injury, where skull- and vertebral- bone marrow cells formed major contributions to CNS-infiltrating monocytes[42]. After additional inflammatory injuries mimicking pathogenic infection with chemical meningitis models, skull-derived neutrophils also infiltrated the CNS via these channels[44].

The exact routes that skull and vertebral bone marrow-derived cells use to enter the CNS parenchyma remain elusive. Where it contacts the dura mater, the arachnoid layer contains arachnoid barrier cells linked by the junctions CLDN11 and E-Cadherin, that is believed to limit trans-arachnoid passage[89]. However, this barrier is not absolute as CSF-delivered tracers traverse this barrier to access the dura, and both dural-derived cytokines and topical skull tracers can access the CNS[2,34,90]. Much like vascular tight junctions are impaired during inflammatory conditions[91], disruption of the arachnoid barrier may permit paracellular leukocyte migration following CNS insults allowing continued migration of the skull and vertebral bone marrow cells. An alternative explanation is that skull and vertebral bone marrow derived cells use similar pathways that enable CSF efflux into the dural meninges at parasagittal regions, and that distinct anatomical features here enable this trafficking. An improved understanding of this route, and methods for its manipulation, could permit mechanisms to limit or augment such passage in CNS injuries where these cells may be beneficial or detrimental.

One important open question is whether immune cells arising from distinct bone marrow sites adopt different phenotypes that can contribute to beneficial or pathological outcomes. To this end, we and others recently performed scRNA-seq skull bone marrow to contrast them to peripheral bones. While similar populations in both bone marrow sites were present, transcriptional differences were apparent in numerous populations, including an enriched migratory gene ontology signature in bone marrow proximal to CNS borders[42,92]. These data suggest that cells arising in different bone marrow sites may already adopt distinct phenotypes, even prior to egress, perhaps shaped by their local environments.

During inflammatory CNS models, for example EAE, distinct infiltrating monocyte subsets have been observed that display protective or pathogenic phenotypes[93]. Transcriptional analysis of myeloid cells isolated from the spinal cord of mice with EAE and spinal cord injury demonstrated that blood-derived monocytes more closely resembled the pathogenic phenotype than those derived from vertebral bone marrow[42]. This suggests the possibility that CNS bone marrowderived cells may represent a more protective subset, and that targeted manipulation of different trafficking routes could represent attractive therapeutic interventions. Conversely, if these skull and vertebral-derived cells are able to infiltrate pathologies in which a pro-inflammatory environment may be beneficial, for example brain tumors, they may be detrimental due to an immunosuppressive phenotype.

Skull bone marrow senses CSF

The skull and vertebral bone marrow dispense immune cells to the brain borders and CNS tissues following injury and neuroinflammation[42,44]. This suggests that these sites are able to sense dysfunction in the underlying tissues. We and others recently demonstrated that much like the dura, the skull bone marrow is able to sample CNS dysfunction via soluble cues present in the CSF through direct connections between the CSF and the bone marrow[35,36]. This skull bone marrow-CSF connection was functionally demonstrated in mice using CSF-delivery of fluorescent tracers and antibodies[35,36], and confirmed in humans with intrathecal gadolinium administration and MRI of skull bone marrow[37]. The exact pathway appears to follow vascular structures distinct from diploic veins and CSF-delivered tracers can be observed in the perivascular spaces surrounding the bridging vessels.

The ability of CNS-associated bone marrow to sample CSF allows these sites to respond to CNS perturbations. Following pathogenic inflammatory insults, including meningitis models induced by CSF delivery of E. coli injections or the gram-negative bacterial component LPS, elevated haemopoietic stem cell proliferation was observed in the skull bone marrow which is critical for immune cell production[35,36]. Further, the recognition of CNS infections via the CSF resulted in elevated differentiation of myeloid precursors from haemopoietic stem cells and the trafficking of mature myeloid cells into the brain borders—likely to assist pathogen clearance[35,36]. Similar to microbial cues being recognized by the skull bone marrow, these sites also sense inflammatory cues resulting from sterile CNS injury. By harvesting CSF of mice that received a spinal cord injury and transferring this to the CSF of naïve mice, we found that inflammatory cues in CSF were sufficient to enhance skull bone marrow myelopoiesis and dural trafficking—as observed after injury—yet without an actual insult[35]. Collectively, these data demonstrate that the skull bone marrow can access CSF-derived cues to keep tabs on the active brain state and respond accordingly to mount a tailored immune response.

Brain border neuroimmunology and CNS disease

Neuroimmune interactions are increasingly recognized in diverse brain disorders[51,94–98]. While a substantial focus has been on the resident brain macrophages, the microglia, the brain borders represent highly active immunological sites that shape homeostatic brain functions and may be critical in the pathophysiology of diverse neurological diseases.

Alzheimer’s disease and aging

Genome wide association studies of late-onset sporadic Alzheimer’s disease (AD) implicated innate immune pathways, including the receptor Trem2, in disease risk[99,100]. As the major immune cell in the homeostatic brain, these genetic polymorphisms are most often attributed to and studied in microglia[101]. However, other myeloid cells in perivascular spaces, the leptomeninges, the dura mater, the choroid plexus, and the skull bone marrow would be similarly perturbed by alterations of these AD-linked genes. Importantly, several of the top susceptibility genes attributed to microglia in mice pertain to vascular cells in humans, supporting an alternative concept of vascular dysfunction in AD and raising important considerations with respect to species differences[102]. Similarly, single-nucleotide

polymorphisms (SNPs) in genes encoding adaptive immune response pathways such as HLA-DRB1—critical in facilitating antigen presentation to T cells—are present in late-onset Alzheimer's disease patients[99,100]. CD4 and CD8 T cells infiltrate the meninges of AD patients and display abundant clonality in the CSF suggesting antigen recognition[51]. T-cell derived factors—including the pro-inflammatory cytokine IFNy—can also impair hippocampal neurogenesis and promote neuroinflammation suggesting the potential for border-derived cytokines in AD-related cognitive decline[103,104]

One of the major hallmarks of late-onset AD is a failure to effectively clear pathological misfolded proteins. Meningeal lymphatics are critical for waste removal from the CNS, including the AD-associated proteins amyloid beta and tau, and their dysfunction promotes the build-up of parenchymal waste and cognitive dysfunction[71,105]. Meningeal lymphatic drainage is perturbed during aging, and is further accelerated in age-matched rodent models of AD[69–71]. Recent works have also demonstrated that appropriate meningeal lymphatic drainage is equally important for correct glymphatic function, CNS immunotherapy, and control of innate CNS immunity[70]. Disruption of meningeal lymphatics in murine models of AD worsened amyloid beta removal by immunotherapy, as well as exacerbating microgliosis, neurovascular dysfunction, and cognitive deficits[70]. Of interest, several AD-related SNPs are also highly expressed by the lymphatic vasculature[70]. While a genetic predisposition is well recognized for microglial dysfunction[99,100,106] and cerebrovascular impairment[48,107,108], the potential for AD-related SNPs to impact lymphatic biology raises intriguing and additional targets for therapeutic benefits in AD[71].

To permit clearance of amyloid beta by the meningeal lymphatics, its efflux to the CSF is essential. Disrupting ISF-CSF exchange, for example by impairing AQP4 astrocyte endfoot polarizations as observed in AD, results in parenchymal amyloid beta build up[109]. Similarly, we recently demonstrated that perivascular macrophages are critical in facilitating CSF movement and ISF exchange through modulating arterial pulsatility[50]. The depletion of these border macrophages in mouse models of AD resulted in impaired ISF removal and exacerbated amyloid beta plaque buildup in the brain.

Recent human positron emission tomography (PET) imaging with Translocator Protein 18 kDa (TSPO) ligands—a commonly utilized modality to suggest inflammatory responses—revealed extensive activation at the skull bone marrow surrounding the brain in human AD patients[92]. Given the recently described bi-directional axis between the CNS and haemopoietic sites[35,36], these data raise the intriguing possibility, that skull bone marrow sense CNS dysfunction in AD, likely through soluble cues present in the CSF. Whether this is beneficial, for example to promote the infiltration of skull-bone marrow derived phagocytes to clear amyloid plaques, remains to be seen.

Multiple sclerosis and autoimmune diseases of the CNS

The immune system has elaborate checks and balances in order to recognize self from non-self, including the elimination of lymphocytes with T cell receptors (TCRs) or BCRs with strong affinity for self-peptides, to prevent autoimmunity. Autoimmune diseases of the CNS result from an overactive, or otherwise perturbed immune response against self-peptides. Multiple sclerosis (MS) is a devastating neurological disease resulting from autoimmune

attack of CNS myelin via infiltrating leukocytes and the most common form of neurological autoimmune or neuroinflammatory disease[110]. This condition is commonly modelled in mice using immunization with myelin antigens resulting in EAE[111,112]. While EAE models do not represent the entire complexity of MS, they do model autoimmunity against myelin proteins and allow the study of autoimmune T cell trafficking across brain barriers[34,54,55].

Abundant immune cell accumulation is observed in the meninges overlying the brain and spinal cord in mouse EAE models and human MS patients[54]. Through constant exposure to CNS myelin antigens, including MOG, MBP, and PLP via CSF-to-dural passage, as well as the presence of specialized antigen presenting cells surrounding the dural sinuses, and in the leptomeninges, myelin reactive T cells can be efficiently reactivated at the border sites promoting an adaptive immune response[34,54]. Additionally, tertiary lymphoid structures, consisting of T cell, B cell, and supportive $CXCL13^+$ stromal compartments are observed in the leptomeninges of MS patients and are important sites in adaptive immune responses and the coordination of local tissue immunity[113].

MS is characterized by immune infiltration into the CNS tissue, promoting demyelinating lesions. Interestingly, the CNS-associated bone marrow can deliver immune cells to the meninges and CNS parenchyma in EAE models, providing a novel route of immune trafficking distinct from blood[42]. Given that human skulls harbor similar channels, these data suggest the possibility of bespoke immune cell trafficking from these bone marrow sites in MS. Recent works utilizing PET imaging of the skull bone marrow via TSPO ligands revealed enhancement in both primary progressive and relapsing remitting MS patients compared to controls, suggestive of an active inflammatory status of this bone marrow in MS patients[92].

The disruption of the meningeal lymphatic system via genetic and surgical approaches, and thus T cell, APC, and tissue antigen drainage, was found to significantly abrogate T cell priming in deep cervical lymph nodes and attenuated EAE pathology[28]. Similar results are observed following resection of CNS-draining lymph nodes, and myelin proteins are found in these nodes in MS patients, exemplifying the importance of T cell priming in these nodes[86,114]. Interestingly, viral overexpression of a VEGF-C/D trap that depletes meningeal lymphatics did not alter pathogenic effector T cell trafficking into the brain or meninges, or the clinical disease score, using adoptive T cell transfer models of EAE[54]. However, as the disease course of these adoptive transfer models differs to that of passive immunization models, it is difficult to directly compare these two models. The full extent of meningeal lymphatic contributions in multiple sclerosis remains to be seen, but it seems likely that meningeal lymphatics and dCLN priming may play a critical role in human MS.

CNS tumors

Glioblastomas are the most common primary malignant brain tumor. These tumors are highly aggressive, treatment resistant, and display exceptionally poor patient prognosis[115]. The factors underlying GBMs are diverse, but one prototypical feature is a failure of immunological rejection via impaired cell-mediated toxicity. This occurs as a result of high expression of checkpoint blockade molecules, factors that prevent T cell mediated attack, and likely inefficient priming of T cells in CNS draining lymph nodes.

The meningeal lymphatic system—through drainage of tumor antigens or neoantigens—represents a critical axis for peripheral recognition of CNS neoplasms. Recent works have elegantly demonstrated how enhancing antigen drainage of CNS tumors via VEGF-C mediated meningeal lymphangiogenesis, combined with checkpoint blockade, promotes tumor rejection through the breakdown of CNS immune privilege[29,32]. These data provide strong evidence suggesting that the meningeal lymphatics at the brain borders can be exploited to enhance immune rejection of CNS neoplasms.

CNS tumors, including gliomas and meningiomas also consist of immune infiltrates, including monocytes, monocyte-derived macrophages, T cells, B cells, neutrophils, and dendritic cells[116–118]. Given the proximity of these masses, particularly meningiomas, to the skull bone marrow it would be intriguing to examine whether the skull bone marrow functions as a source of immune infiltrates in these tumors. Recent transcriptional and methylation profiling of human meningiomas observed distinct subtypes with genetic mutations and epigenetic and gene expression profiles[119]. One subtype displayed altered methylation patterns and transcript expression for genes relating to immune infiltration and meningeal lymphatics, including HLA-transcripts and LYVE1[119]. These data implicate a role for meningeal lymphatics and antigen presentation in brain border regions for this intracranial tumor.

Cerebrovascular disease

The brain is a highly metabolic organ and correct functioning requires appropriate vascular maintenance. As important relay sites between the CNS and periphery, perivascular and leptomeninges macrophages surrounding the cerebrovasculature are critical in integrating peripheral signals and relaying these to the brain. However, recent works have also described how immune interactions at the CNS borders can initiate vascular disruption and promote perturbed neuronal function in diverse states[120–123].

Ischemic stroke, and post-reperfusion injury, promote severe brain dysfunction through vascular disturbances. Recently, a role for brain border macrophages in facilitating continued vascular disruption and neurological sequalae was observed[122]. Following experimental stroke using a middle cerebral artery occlusion, perivascular macrophage-derived VEGF was elevated and contributed to leptomeningeal and cerebrovascular permeability that worsens acute neurological dysfunction[122]. Additionally, after a stroke, these border-associated macrophages produce diverse chemoattractants that facilitate granulocyte recruitment which can further disrupt cerebrovasculature through the generation of oxidative stress[122].

Macrophage-mediated reactive oxidative species production is a common phenotype in additional vascular disorders, including hypertension, a critical risk factor for vascular dementia and cognitive impairment[124]. In mouse models of hypertension, border associated macrophage superoxide production results in oxidative vascular stress and blood-brain barrier (BBB) disruption[120]. Specific ablation of these perivascular macrophages via clodronate liposome delivery attenuated the detrimental effects of macrophage-mediated oxidative stress, as did deletion of macrophage Ang II type-1 receptor, which is critical in vasoconstriction[120,121]. Similarly, depletion of border macrophages limits amyloid-

mediated oxidative neurovascular dysfunction in models of cerebral amyloid angiopathy and AD[91,125,126].

A recent single cell RNA-sequencing atlas mapped the cellular and transcriptional profile of malformed human brain vasculature and provided insights into immune-related mechanisms[123]. Here, they demonstrated extensive immune cell accumulation in brain arteriovenous malformations—pathological connections between arteries and veins[123]. Interestingly, both $CD11c^+$ APCs and T cells (CD4 and CD8), were present in these lesions, suggesting the potential for active antigen presentation and adaptive immune contributions.

While the aforementioned studies largely suggest perivascular macrophages are detrimental to vascular function, these cells can also contribute to vascular repair. After meningeal vascular injury induced by traumatic brain injuries, macrophages contribute to wound healing by scavenging fibrin promoting angiogenesis, and recruiting myeloid cells that remove dead cells in the lesion core[127].

Future perspectives

Recent studies focusing on the brain borders have illuminated the diverse role of these tissues in neuroimmune communications. Several key points, however, need to be addressed prior to translating these new concepts into meaningful therapeutic agents.

One of the mysteries in communication between the brain and its borders is the permeability, or lack thereof, of arachnoid and dural barriers. These layers supposedly prevent fluid exchange between sub-arachnoid space and the dura. This argument has been empirically refuted in rodents and humans, as CSF-delivered tracers and/or endogenous CNS-derived peptides are found in the dura, in the skull bone marrow, and are drained to deep cervical lymph nodes via meningeal lymphatics located in the dura mater[34–37,61,65,66]. However, the route that molecules take between these compartments is not understood. Our current working model is that the CSF exchange with the dura mater is taking place throughout the perivascular space surrounding cerebral veins that penetrate the arachnoid barrier as they drain into the dural sinuses. These routes could also explain how molecules produced in the dura could reach the parenchyma, although additional specialized sites through the arachnoid, or the existence of a trans-arachnoid movement of cargo may also exist. Understanding the routes that molecules take from the dura to reach the CSF/brain and, conversely, from the brain to reach the dura would not only shed a new light on neuroimmune interactions under physiology and in pathological conditions but will also allow development of new delivery systems for therapies to the brain.

Although we focus our attention on meningeal routes for waste removal from the brain, it should be emphasized that the BBB exists not only to prevent blood-borne molecules to enter the parenchyma, but also to export molecules from the parenchyma to the blood. The clearance of amyloid beta in AD via LRP-1-mediated transcytosis is one such example[107,128,129]. While disruption of meningeal lymphatic drainage was found to impair the clearance of parenchymal Aβ[70,71], this may be a result of a direct impairment of clearance due to dysfunctional lymphatics, or could be the result of

impaired BBB function, secondary to lymphatic impairment. Indeed, we recently observed that a dysfunctional meningeal lymphatic promotes transcriptional changes in the brain vasculature[70]. Understanding how different outlets of brain clearance systems are linked together would be important to design future therapies and their delivery methods.

The next decade or so will likely be devoted to the development of immune-based therapeutic approaches for brain disorders. Anti-amyloid antibodies have already been shown to remove the plaques efficiently[130] although such treatments often display adverse side effects[131,132]. Combination therapies incorporating aspects of brain border immunity, including augmenting meningeal lymphatic function, could be utilized for a more efficient elimination of the soluble oligomers as well as other potential toxic metabolites[70].

Likewise, T cells at the brain borders are of a potential therapeutic interest. Recent works have demonstrated that anti-viral T cells are found in the CSF of AD patients and suggested that these cells are active participants in disease progression[51,103]. These cells, however, may just be bystanders and their presence in the meninges may simply result from exposure to diverse infections throughout life. Such accumulation of anti-pathogen T cells might have decentralized meningeal immunity—that is, caused the displacement of beneficial homeostatic T cells by additional populations—leading to altered immune cell secretions and associated cognitive dysfunction. Instead of T cell suppression in this case, we may need to reset or modify the T cell compartment. Understanding the “healthy” T cell meningeal repertoire and generating T cells that would aid under different pathologies may be the next frontier in brain immunotherapy.

When immunotherapy was proposed for cancer therapy, it was met with skepticism[133]. Over the last two decades however, it has transformed the therapeutic approaches to cancers and offered new hope for patient treatment for neurological disorders including multiple sclerosis, autoimmune encephalitis, and neuro-psychiatric lupus[134–136]. It is our hope that inspired by these success stories, neuroscientists will continue to embrace immunotherapy and manipulation of the immune system, for additional neurological disorders to provide meaningful therapy for patients. While targeting specific immune cells will likely be insufficient to cure complex brain disorders, immune-based approaches, including those targeting the cells at the brain borders, may alleviate the suffering and hopefully delay the onset of these devastating disorders.

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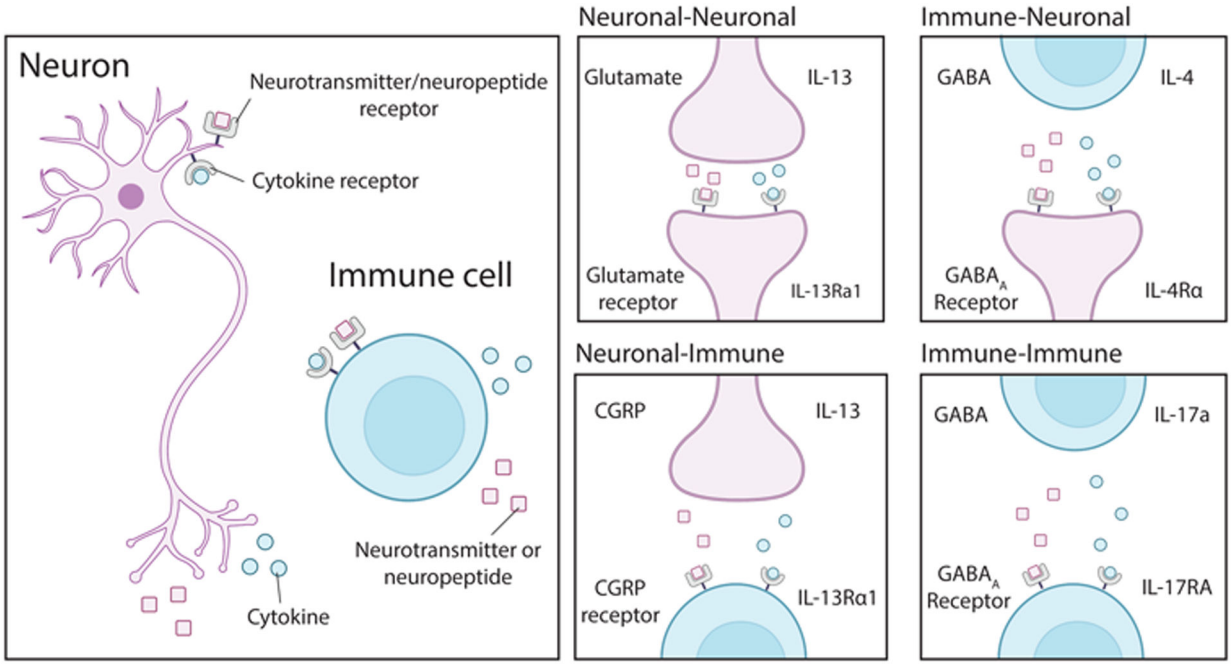

Figure 1 Ⅱ. Neuro-immune cross talk.

Cells of the central nervous system and immune systems communicate using numerous different signaling molecules. Cells of the immune system primary communicate via cytokine signaling on cytokine receptors but can also secrete and respond to molecules used by the central nervous system including neurotransmitters and neuropeptides. Conversely neurons in the central nervous typically communicate via neurotransmitters and neuropeptides but can also secrete and respond to cytokines via expression of cytokines themselves or cytokine receptors.

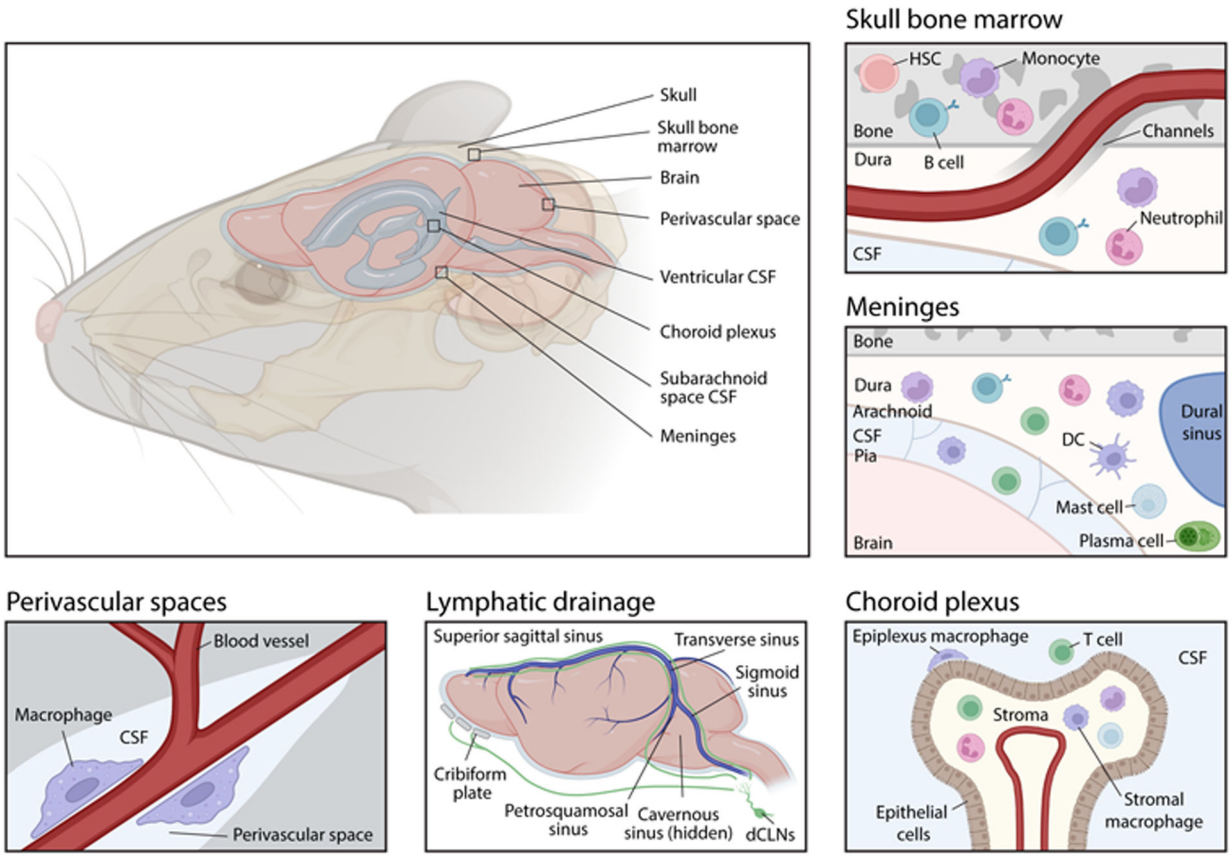

Figure 2 Ⅱ. Anatomical sites for neuroimmune interactions at the brain borders.

The brain is surrounded by several distinct anatomical sites in which neuroimmune crosstalk can occur. The meninges represent a triple-layered membranous structure and surround the brain. Overlying the meninges, the skull contains bone marrow that is functionally connected to the meninges and underlying brain. The choroid plexus is situated within the ventricles of the brain. Numerous lymphatic efflux routes exist for the drainage of brain interstitial fluid via the cerebrospinal fluid. Perivascular spaces exist surrounding penetrating brain vasculature that contain cerebrospinal fluid and resident immune cells.

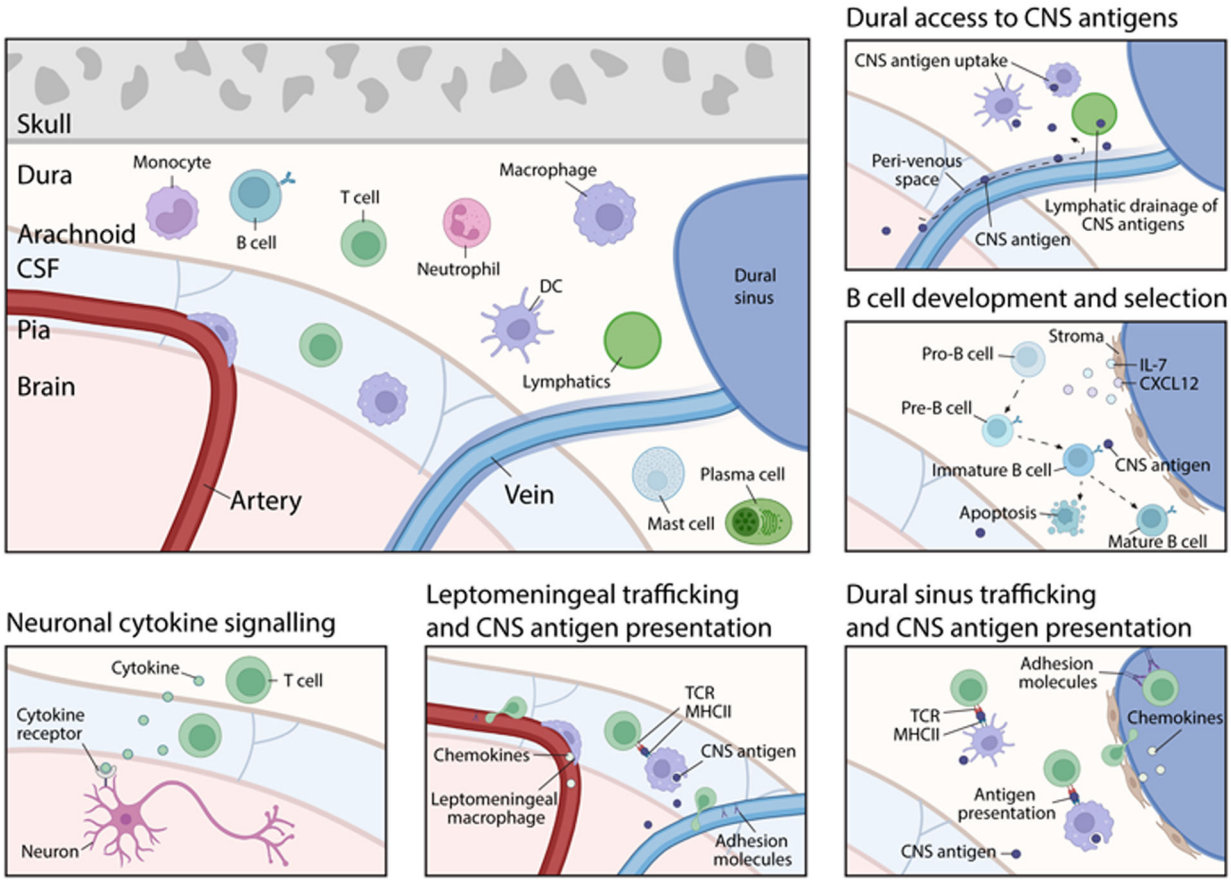

Figure 3 Ⅱ. Meninges and neuroimmune interactions.

The meninges contain diverse immune populations that contribute to neuroimmune responses. Immune cells, including T cells, are situated in the dura mater and leptomeninges and produce cytokines that can signal onto neuronal cytokine receptors to alter firing patterns, alter neuronal connectivity, and control behavioral outcomes. Specialized vasculature in the meninges enables continuous T cell trafficking and interactions with resident antigen presenting cells. CSF continuously has access to the different meningeal layers, enabling T cell responses to brain derived antigens from the meninges allowing them to respond to brain perturbations. Recognition of these brain-derived antigens enables elimination of autoreactive B cells in the meninges to CNS-specific antigens. CSF efflux to the dura mater also enables it to be drained via a lymphatic network that exist in this layer to superficial and deep cervical lymph nodes for additional CNS immune surveillance and removal of CNS waste products.

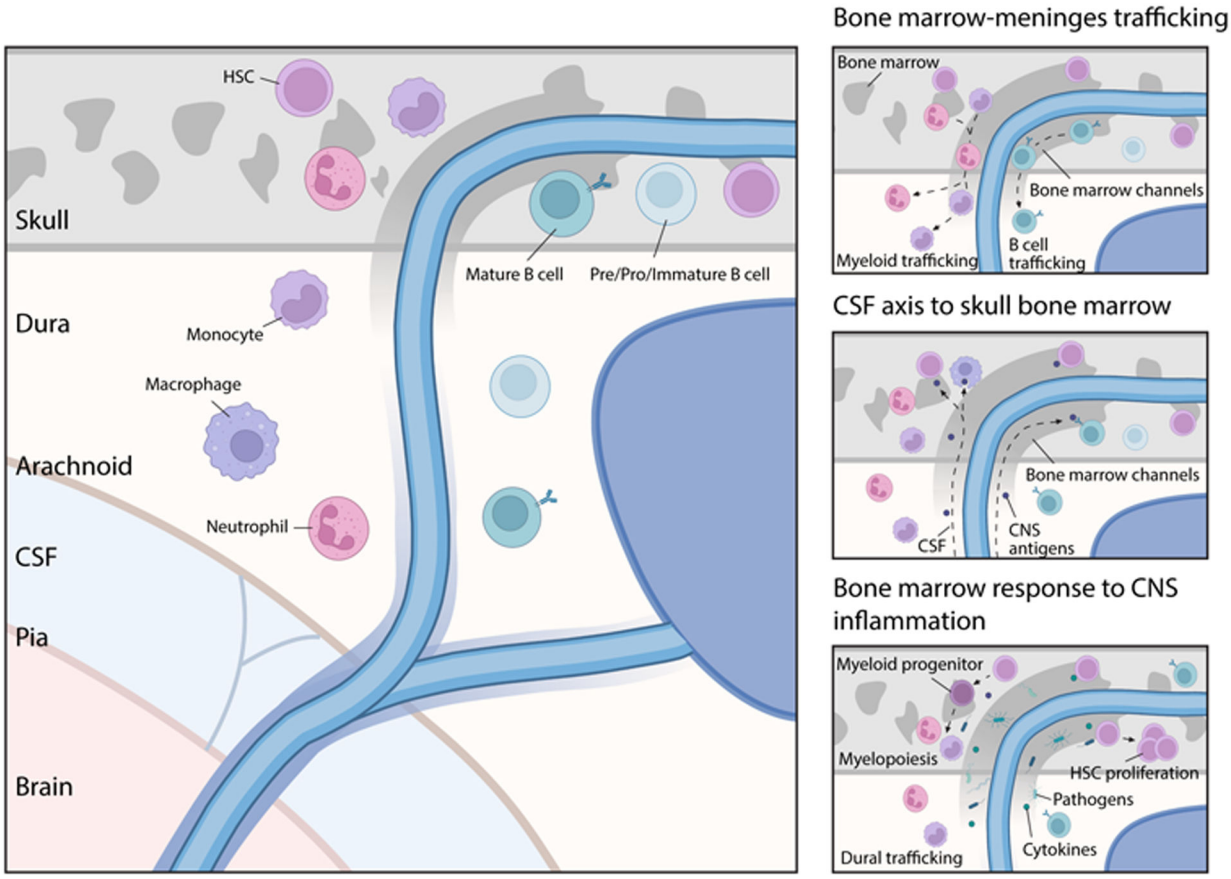

Figure 4 Ⅱ. Skull bone marrow and neuroimmune interactions.

A large pool of bone marrow is situated at the brain and spinal cord borders in the skull and vertebrae. Via channels that directly connect the bone marrow with the underlying dura mater these two layers are intimately connected. Under homeostasis, immune cells produced in the skull bone marrow, including B cells, monocytes, and neutrophils can utilize these channels to traffic into the dura mater. Under pathological conditions, these cells can further traffic to underlying leptomeninges and the brain and spinal cord parenchyma. These dural channels also allow CSF access to the skull and vertebrae bone marrow. Under homeostasis, CSF-derived ligands shape bone marrow cell phenotypes and under pathological conditions, including sterile injuries and infectious pathogens, inflammatory changes in the CSF alter hematopoiesis in the CNS-associated bone marrow to enhance immune cell production.