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Brief Reviews

The dura mater: A hub for immune surveillance at the central nervous system borders

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Abstract

The outer layer of the meninges, the dura mater, forms a critical interface at the border of the central nervous system (CNS). While historically the dura was viewed as a protective physical barrier for the brain and spinal cord, providing structural support for the venous sinuses, more recent research has shown that it is intimately connected to adjacent bones, CNS organs, the systemic circulation, and peripheral organs, particularly the gastrointestinal tract, via immune cell immigrants. In parallel, advances in immunophenotyping have revealed that the dura houses a plethora of immune cells, some within aggregates in dural-associated lymphoid tissue that can support the activation of adaptive immune cells, including germinal center responses. These dural immune cells can acquire immunological information from the network of dural blood and lymphatic vessels, as well as autonomic and sensory nerves, and newly discovered arachnoid cuff entry points provide a direct connection with the subarachnoid space. In this review, we will summarize recent evidence that highlights the dura as a hub for the detection, integration, and relay of immune signals from outside and inside the CNS.

Keywords: dura mater, dural-associated lymphoid tissue, DALT, gut-dural axis

Introduction

The function of the brain requires continuous acquisition of information from peripheral organs and the external environment, and the reciprocal relay of instructions via the motor, autonomic, and endocrine systems to ensure an appropriate response that maintains organismal homeostasis and survival. While historically, the meninges have been viewed as an inert protective layer that encases the organs of the central nervous system (CNS), emerging evidence points to a more complex role as an immune hub at the border of the CNS. In this review, we will focus on emerging evidence that the dura mater, the outer layer of the meninges, contains a rich network of immune cells, including migrants from the gastrointestinal tract and adjacent calvarial bone marrow. These dural immune cells are able to sense and respond to local and systemic immunological signals due to the presence of a fenestrated vasculature, and specialized anatomical structures that connect it to the skull and vertebral bone marrow above and cerebrospinal fluid (CSF) and leptomeninges beneath, the latter providing a means of communicating the prevalent immunological context to the brain. Together, this points to a new view of the dura as anything but inert, and rather as an active center for the integration and relay of immunological information.

Dural structure and immune composition

The trilayered meninges are composed of an outer dura mater, middle arachnoid mater, and inner pia mater that together encase the brain and spinal cord. The dura mater is a fibrous structure formed from a periosteal layer that lies adjacent to the skull, and a meningeal layer facing the arachnoid, with large venous sinuses located between the two layers that drain venous blood from the brain, skull bone marrow, and subcutaneous scalp.[1] Beneath the dura, the arachnoid mater forms a tight, barrier that encloses the subarachnoid space, a fluid-filled compartment containing CSF. The innermost pia mater, is a thin, permeable layer that closely follows the brain's contours, allowing limited CSF interaction with the parenchyma.[2] The arachnoid and pia together constitute the leptomeninges. CSF is produced by cells of the choroid plexus, located within the brain's ventricles, and circulates from the lateral ventricles, to the third and fourth ventricles, then into the subarachnoid space or the central canal of the spinal cord.[3] Beyond buoying the brain, CSF plays a key role in waste clearance via the glymphatic system, a perivascular network dependent on AQP4 water channels expressed on astrocytic endfeet.[4,5] This system, enables the exchange of molecules between the brain parenchymal interstitial fluid and CSF, providing a means of flushing out neurotoxic waste during sleep.[6] Dysfunction in glymphatic drainage is linked to neurodegenerative diseases and is associated with accumulation of toxic forms of amyloid-β in the brain in murine models of Alzheimer's disease.[7]

The blood supply of the dura comes from the middle meningeal artery (arising from a branch of the external carotid artery in humans), and forms a dense vascular network

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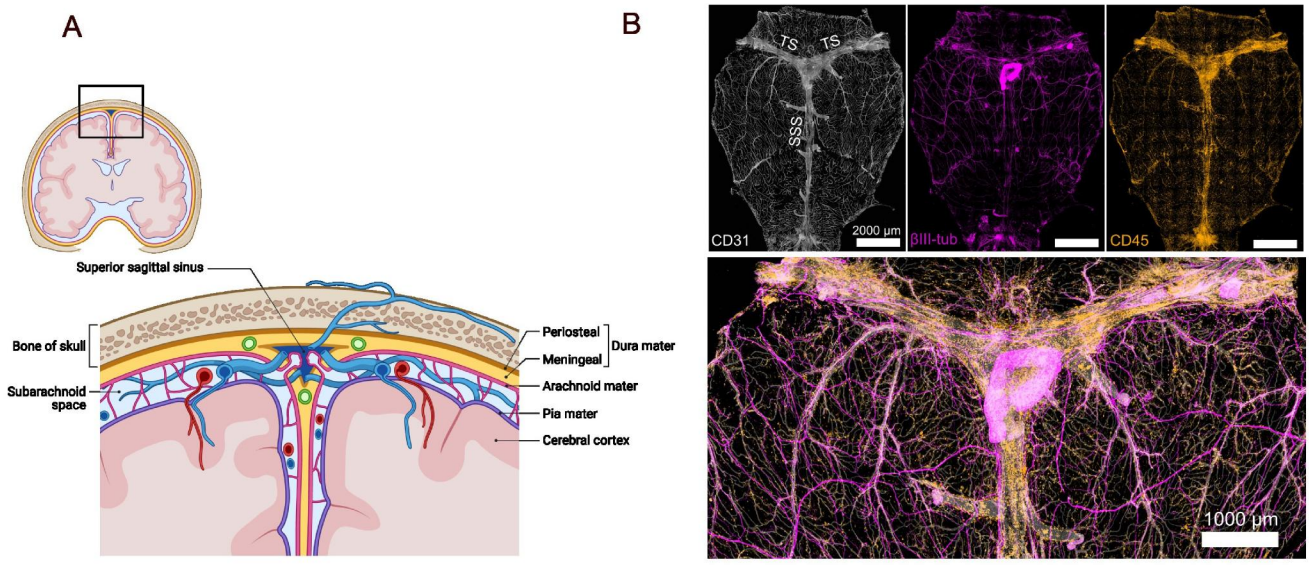


Figure 1. Anatomy of the meninges and dura mater. (A) Schematic showing the 3 layers of the meninges that encase CNS organs. (B) Whole-mount imaging of mouse dura mater. Vascular endothelial cell staining (CD31, white) demonstrates large dural venous sinuses (superior saggital sinus [SSS]) and transverse sinuses (TS). Nerves were stained with βIII-tubulin (magenta) and immune cells with CD45 (yellow).

between the periosteal dura mater and skull bone, ultimately draining into the dural venous sinuses (Fig. 1).[8] The dural vasculature expresses PLVAP (also known as PV1),[9,10] a key structural component of fenestrae, but not the tight junction proteins found in brain vascular endothelium, such as claudin-5 and occludin.[11,12] In addition to this fenestrated vasculature, lymphatic vessels also travel through the dura, draining to the deep cervical lymph nodes.[13] These meningeal lymphatics were visualized using Prox1-Tdtomato reporter mice combined with immunofluorescence staining and intravital two-photon imaging of CSF tracer dye clearance and play a critical role in the removal of brain parenchymal-derived pathological proteins such as amyloid-β.[14] The dura also contains a rich network of autonomic and sensory nerves, some of which track dural vasculature (Fig. 1), and include CGRP+ nociceptor neurons that project from the trigeminal ganglia.[15]

Several studies using flow and mass cytometry, as well as single-cell RNA sequencing, have characterized the immune composition of the dura. In sum, these demonstrate that the dura is the most immune cell rich of the CNS border tissues, housing a heterogeneous network of both innate and adaptive immune cells.[16–19] Immunophenotyping using methods that require the generation of single-cell suspensions inevitable underestimate the frequency of some cell types, particularly large, structurally integrated, sessile cells such as macrophages, and also fails to delineate their anatomical location. Thus, the parallel use of image-based immunophenotyping has provided critical additional information. In the case of mouse dura, its size is readily amenable to wholemount imaging enabling a global overview of the location of immune cells. These imaging studies revealed that immune cells are not uniformly distributed across the dura but are concentrated around the venous sinuses and vasculature (Fig. 1), with important implications for how these cells acquire immunological information. Macrophages are the most abundant immune cell population in the dura, closely adhering to the walls of the venous sinuses but also distributed more broadly through the nonsinus dura (Fig. 2). Dural macrophages can be divided into two subsets based on major histocompatibility complex class II (MHC II) expression.[20,21] They originate from erythromyeloid progenitors in the yolk-sac, similar to microglia,[22,23] but are slowly replaced in adulthood by monocytes, forming an MHC II^{hi} population,[18] with the potential for antigen presentation to CD4 T cells.

Adaptive immune cells are predominantly located adjacent to the venous sinuses, with larger clusters evident in specific anatomical locations. We called these T and B cell lymphoid aggregates dural-associated lymphoid tissue (DALT) (Fig. 3A), with the largest of these structures located anteriorly at the rostral-rhinal confluence of the sinuses and lymphatic vessels,[24] and evident at postnatal day 8, before the formation of the superior sagittal sinus. The presence of this structure in early life and in homeostasis without any overt pathological stimulus supports its designation as a secondary lymphoid structure, analogous to mucosal-associated lymphoid tissues. In *Rorc*-deficient mice, rostral-rhinal lymphoid aggregates are sparce, suggesting that lymphoid tissue-inducer cells are required for the organization of DALT. The rostral-rhinal DALT contains podoplanin^{+} fibroblastic reticular-like cells, dendritic cells (DCs), and macrophages, as well as GL7^{+} germinal center (GC) B cells, CD4 T cells, and plasma cells, even in the absence of overt infectious or pathological challenge. Spatially, different cell subsets within DALT clusters were relatively intermingled, and exclusive B and T cell zones were not observed. However, B cells predominated more centrally, surrounded by T cells, with plasma cells also localized to the periphery of areas containing GC B cells and CD4 T cells, an arrangement not dissimilar to intestinal cryptopatches or isolated lymphoid tissues.[25] Immune cell clusters within DALT increased with age,[24,26] and analogous perivascular lymphocyte aggregates were also identified in human dura.[24]

Dural surveillance of circulating stimuli

The fenestrated vasculature within the dura allows molecules within the peripheral circulation to be sensed and sampled by perivascular immune cells.[24,27] The rostral-rhinal DALT in particular provides a hub where intravenously administered fluorescently labeled dextran or inert beads accumulate and

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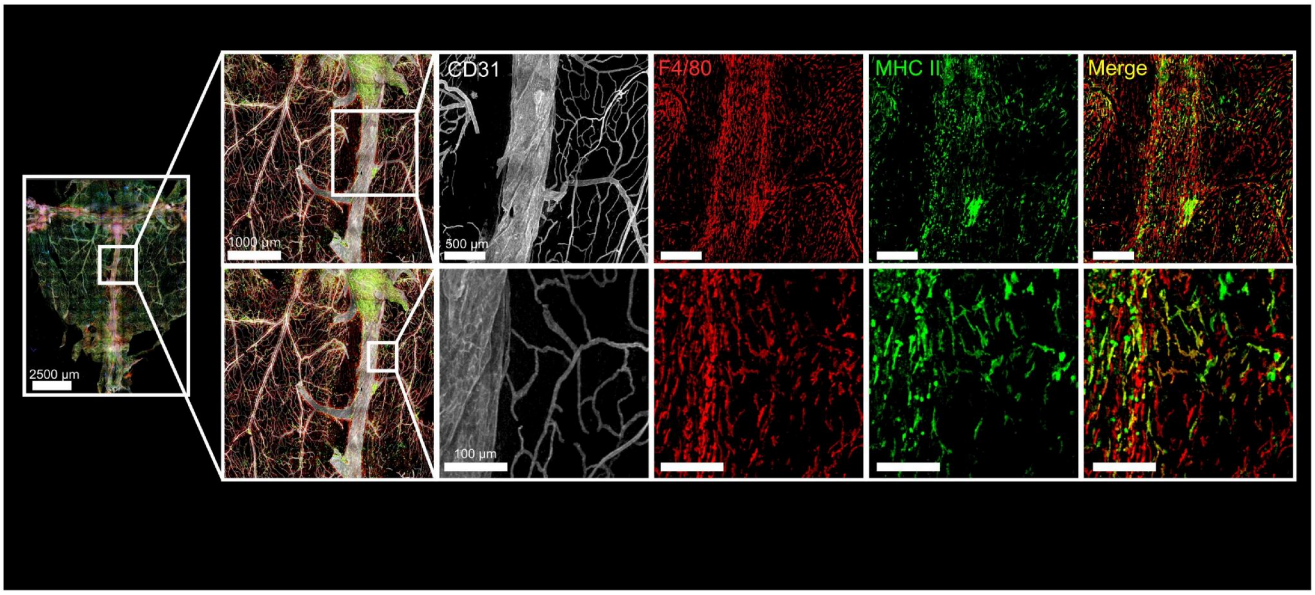


Figure 2. Macrophages form the major immune population in the dura. Whole-mount immunofluorescence imaging of the superior sagittal sinus showing that macrophages (F4/80+, red) densely populate the dura and include MHC II (green) high and low population.

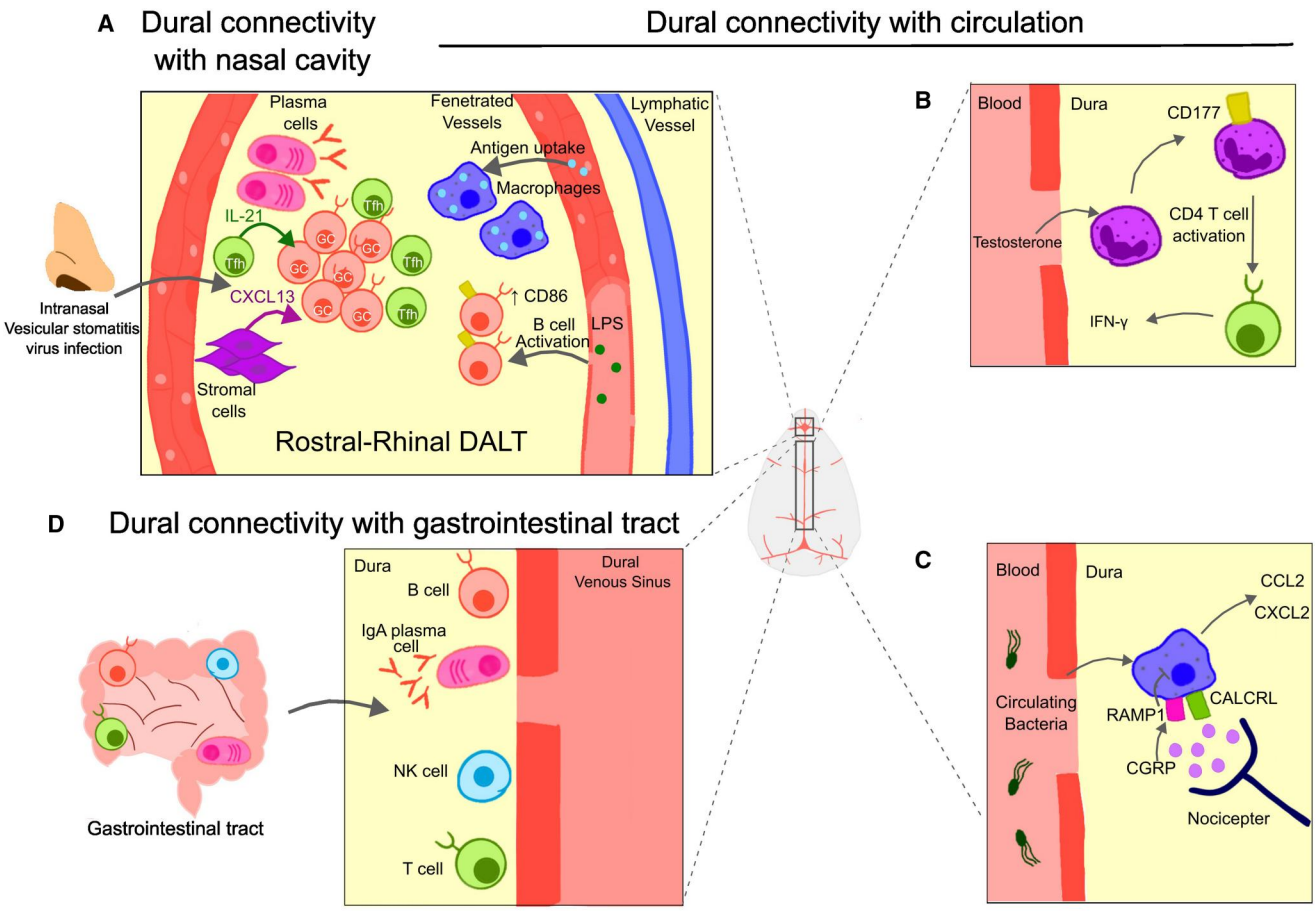


Figure 3. Dural connections with circulation, nasal cavity, and gastrointestinal tract. (A) Aggregates of immune cells in DALT in the rostral-rhinal area surrounded by fenestrated vasculature, enabling myeloid cell uptake of circulating antigens, and B cell activation by intravenous lipopolysaccharide. Intranasal challenge with VSV leads to the development of GC responses, with an expansion of CXCL13-expressing stromal cells, IL-21–producing T follicular helper and GC B cells, and plasma cells (B). Neutrophils upregulate CD177 in response to an increase in circulating testosterone, promoting T cell activation. (C) Dural macrophages can internalize and respond to circulating bacteria by upregulating CCL2 and CXCL2. This activation can be attenuated by CGRP secreted by local nociceptor neurons. (D) Gut B, plasma, NK, and CD4 T cells migrate to the walls of the dural venous sinuses.

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are rapidly taken up by local macrophages, with 0.2 μm beads more efficiently taken up than 2 μm beads (Fig. 3A).[24] There is evidence not only for the uptake of circulating antigens within the rostral-rhinal DALT, but also of immune cell activation in response to intravenous stimuli; 7 d following challenge with intravenous lipopolysaccharide, a key component of gram-negative bacteria, B cells within DALT showed increased proliferation and expression of compared with stimulatory molecules.[24] Interestingly, immune cell aggregates within the rostral-rhinal DALT increased in size with age in specific pathogen–free mice that were not exposed to any specific infectious or inflammatory challenging,[24] suggesting that these immune hubs are continuously surveying and responding to circulating or local stimuli.

Beyond the rostral-rhinal DALT, along the walls of the superior sagittal sinus, B cells and IgA-secreting plasma cells increased in number after administration of intravenous *Candida albicans*. The secreted IgA entrapped blood-borne fungi in the perisinus region, preventing their movement into the dura and brain.[28] Perivascular macrophages are also poised to detect and respond to blood-borne bacteria, orchestrating neutrophil and monocyte recruitment following challenge with intravenous *Streptococcus pneumoniae* via *Ccl2* and *Cxcl2* production.[29,30]

Remarkably, dural cells can also respond to circulating hormones (Fig. 3B). In male mice, social threat cues were associated with increases in testosterone, and the combination of stress and androgens resulted in meningeal neutrophil activation and upregulation of CD177, which in turn promoted dural T helper 1 (Th1) IFN-γ secretion.[31] The production of IFN-γ by dural T cells enhanced intrinsic GABAergic inhibition within the prelimbic cortex, blunting neural responses to threatening stimuli. Previous reports have also shown that dural T cell-derived IFN-γ may influence dural lymphatics,[32] in addition to effects on neurons.[31,33]

Dural immune sensing of nociceptor activation

The dura has a dense network of neurons, including CGRP+ nociceptors. CGRP mediates its effects via a heteromeric receptor composed of a G-coupled protein receptor calcitonin receptor-like receptor (CALCRL) and RAMP1. In homeostasis, single-cell RNA sequencing profiling identified *Calcrl* and *Ramp1* expression in dural neutrophils, monocytes, and macrophages, as well as in dural vascular smooth muscle cells.[29] Communication between nociceptors and dural macrophages has been investigated in the context of intravenous challenge with *S. pneumoniae*, in which CGRP suppressed macrophage production of chemokines in the context of bacterial infection (Fig. 3C).[29] This axis was hijacked by *S. pneumoniae*, with bacterial-derived pneumolysin activating nociceptors to release CGRP that attenuated immune cell recruitment via macrophage inhibition, facilitating bacterial CNS invasion. This work nicely illustrates how dural immune cells can integrate information from local neurons to modulate responses to circulating stimuli.

Dural surveillance of nasal immune challenge

The dura not only lines the roof of the calvarium, but also the base of the skull, including the cribiform plate, a pocked piece of bone with holes that allow olfactory nerve fibers to transit from the nasal cavity to the brain. The initial description of rostral-rhinal DALT also noted immune cells surrounding the vasculature in the falx cerebri between the olfactory lobes, and even extending down to the area above the cribiform plate.[24] Intranasal challenge with vesicular stomatitis virus (VSV), a neurotropic virus, resulted in a marked expansion of immune cells in rostral-rhinal DALT, with an increase in CXCL13-expressing stromal cells, and the development of a GC response, supporting local class-switching and somatic hypermutation in B cells (Fig. 3A). The entry of naïve VSV-specific B cells was inhibited by blocking VLA4/LFA1, but once a GC reaction had been initiated, no further input of circulating cells was required to sustain a GC response within rostral-rhinal DALT. Single-cell RNA sequencing of the rostral-rhinal hub following nasal challenge with VSV confirmed the presence of GC B cells, as well as IL21+BCL6-expressing T follicular helper cells and even a small number of *Foxp3*-expressing T follicular regulatory cells.[24]

Dural immune connectivity with peripheral organs

As noted previously, dural lymphocytes predominantly localize to the perisinus regions and to the rostral-rhinal DALT. This location adjacent to fenestrated vessels places them in prime position to respond to circulating immune challenges. A cardinal feature of adaptive immunity is the capacity for memory, enabling more rapid responses upon rechallenge, but how might the dura, an internal sterile barrier, accumulate memory cells or class-switched antibody-secreting cells that could recognize blood-borne pathogens? One solution to this problem is for the dura to acquire lymphocytes that have been activated or primed in the gut, as the commonest source of microbes that invade the blood-stream is the gastrointestinal tract (Fig. 3D). This linked gut-dural immunity was first demonstrated for humoral immunity, with B cell receptor (BCR) sequencing showing a 20% overlap between small intestine and dura, with several clones showing proximal BCRs within intestinal tissue, and BCRs with additional mutations in the dura.[28] Consistent with this shared repertoire, the gut microbiome can profoundly influence dural humoral immunity. For example, treatment with oral antibiotics reduced the number of perisinus dural IgA plasma cells, and reconstitution of the gut of germ-free mice with fecal microbiomes from two different human donors altered the frequency IgA versus IgG plasma cells in the dura.[28]

Similarly, some dural natural killer (NK) cells are gut derived, and their capacity for IFN-γ secretion influenced by the gut microbiome. Photoconversion of the small intestine using Kaede mice demonstrated that gut-derived NK cells comprised around 3% of dural NK cells 24 h later, and oral antibiotic treatment substantially reduced *Ifng* expression in photoconverted dural NK cells.[34] A recent study showed that oral antibiotics also reduced the number of CD4 T cells in dura,[35] and used photoconversion of the whole intestine to show relocation of CD4 T cells from the gut to the extravascular space of the brain, although the dura was not assessed in this experiment. In the context of a CNS pathology, ischemic stroke, the distal intestine of photoconvertible KikGR33 mice was exposed to violet light allowing gut-derived B and T cells to be tracked to the leptomeninges and dura, with photoconverted cells making up 0.3% of dural lymphocytes at 16 h.[36] A more recent study showed that in the absence of

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regulatory T cells, microbiota-specific CD4 T cells can infiltrate the brain causing neuroinflammation, and were also observed in the dura.[37] Thus, it is now clear that both innate and adaptive lymphocytes originating in the gut become localized to the extravascular space of the dura. For B cells, it seems this migration occurs tonically in homeostasis, for NK cells and CD4 T cells, dural trafficking may require either CNS inflammation or gut perturbations, or both, as the photoconversion experiments to date have all involved exposure of the intestine in the context of a laparotomy, which cannot be considered a homeostatic state.

Many questions remain about this axis, including which chemokine signals attract gut cells to the dura? Does a similar gut-dural migration axis apply to CD8 T cells? Are lymphocytes activated in different regions of the gut equally likely to form dural immigrants? What route do lymphocytes take to get from the gastrointestinal tract to the dura and do they preferentially go to DALT versus other sites in the dura? Do gut-derived immune cells also seed to other lymphoid organs? With regards to the broader, related question of how any immune cells enter the dura, Rustenhoven et al.[12] transferred GFP-expressing CD4 T cells into $Rag2^{-/-}$ mice to allow direct imaging of a wave of de novo migration into the dura. Using live imaging of the confluence of the sinuses in craniotomized mice, they observed T cells adhering to sinus endothelium in a P-selectin–, VCAM1-, and ICAM1-dependent manner, and even extravasating through the wall of the sinus into the dura. Using parabiotic mice, they found a 50:50 equilibration of host and donor cells after 1.5 mo.[12] Furthermore, perivascular mural cells (pericytes and smooth muscle cells) are critical negative regulators of T cell entry into the dura during inflammation.[38] Thus, one possibility is that lymphocytes mobilize from the gut into the blood stream and enter the dura via the sinuses. However, the discovery of dural connections with both the overlying skull bone marrow and underlying leptomeninges (discussed subsequently), opens up the possibility of alternate entry routes.

Regardless of how gut-derived immune cells get to the dura, their presence has implications beyond a role in defense against circulating pathogens. The movement of cells from this peripheral organ affords an opportunity to bring information about the prevalent immune challenges and inflammatory state in the gut to the CNS, with cytokine secretion providing a method of communicating this state to the brain. Thus, we propose that the gut-dural immune cell axis potentially acts as an information-relay system for the CNS, reporting on immunological events in a peripheral organ.

Dural immune connectivity with the skull bone marrow

The diploic venous system drains the calvarial bone marrow, traveling via transosseous channels to the dura on route to the venous sinuses. The space around these vessels provides a direct skull-dural connection enabling cell migration into the meninges (Fig. 4A). This was initially described in the context of aseptic meningitis and stroke models, but subsequently observed in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, with neutrophils and monocytes moving from skull bone marrow to dura and even underlying brain parenchyma.[39–43] More recently, Cugurra et al.[42] showed using parabiosis, calvarial bone-flap transplantation, and selective skull bone marrow chimeras that in homeostasis, the calvarial bone marrow was predominantly responsible for replenishing monocytes directly to the dura via these channels, rather than via the circulating pool. Furthermore, single-cell RNA-sequencing revealed that calvarial-derived monocytes were potentially less proinflammatory than their blood-derived counterparts.[42] Advanced imaging techniques including micro-computed tomography, 3D imaging of cleared tissues, and two-photon imaging revealed around 1,000 bony channels between the mouse calvarial bone marrow and the dura. This includes connections to the rostral-rhinal DALT, which sits in an indentation on the underside of the skull. Tissue clearing and light sheet fluorescence imaging also identified skull-meningeal connections in humans, with myeloid cells observed within some of these channels around diploic veins. These transosseous channels were most frequently observed in the parietal skull bone, with ~1,000 channels per cm^2, measuring 40 to 90 μm in diameter, but some of the larger channels measuring >150 μm in diameter.[44] Thus, in both mouse and humans there are multiple highways that calvarial bone marrow cells may utilize to travel to the dura.

It is not only myeloid cells that migrate from skull bone marrow to dura, and also B cells have also been directly imaged within these transosseous channels, likely attracted by CXCL12 expression by dural fibroblasts.[45,46] These immigrants include developing B cells, from the pro-B to immature B cell stage, leading to the hypothesis that the dura may be a site of negative selection for autoreactive B cells recognizing CNS antigens.[45–49] Consistent with this, myelin oligodendrocyte glycoprotein (MOG), a CNS protein and target for autoreactive T and B cells in multiple sclerosis, is expressed in mouse meninges and MOG-specific B cells were underrepresented in dura compared with skull or femoral bone marrow in a MOG-BCR transgenic mouse.[45,46] Genetic deletion of *Mog* restored this MOG-specific B cells in the dura. In older mice, an increased number of age-associated B cells, as well as IgG and IgM plasma cells, were observed in the dura, but these populations appeared to arise from blood rather the skull bone marrow cells.[46]

Dural connectivity with the CSF and leptomeninges

A number of studies observed that administration of tracers or antigens, such as ovalbumin, into the CSF via the ventricles or cisterna magnum led to their accumulation around sinuses and uptake by antigen-presenting cells (APCs), including dural macrophages and DCs (Fig. 4Bi). These APCs were able to present CSF-derived antigen to local CD4 T cells.[12,20] Mast cells are also found in the dura in homeostasis[50] and intracisternal injection of FITC-conjugated anti-c-Kit antibody led to labeling of dural mast cells, again demonstrating that molecules within the CSF can be accessed by dural-resident cells. Indeed, tracers administered into the CSF have also been identified in the skull bone marrow as well as in the dura, emphasizing the extent of connectivity between the dura and its surrounding structures.[43,51]

Despite this accumulating evidence that CSF molecules could be accessed by dural immune cells, the precise route by which this occurred was unknown. A groundbreaking study from the Kipnis group resolved this question, identifying arachnoid cuff exit (ACE) points (Fig. 4B), perivascular

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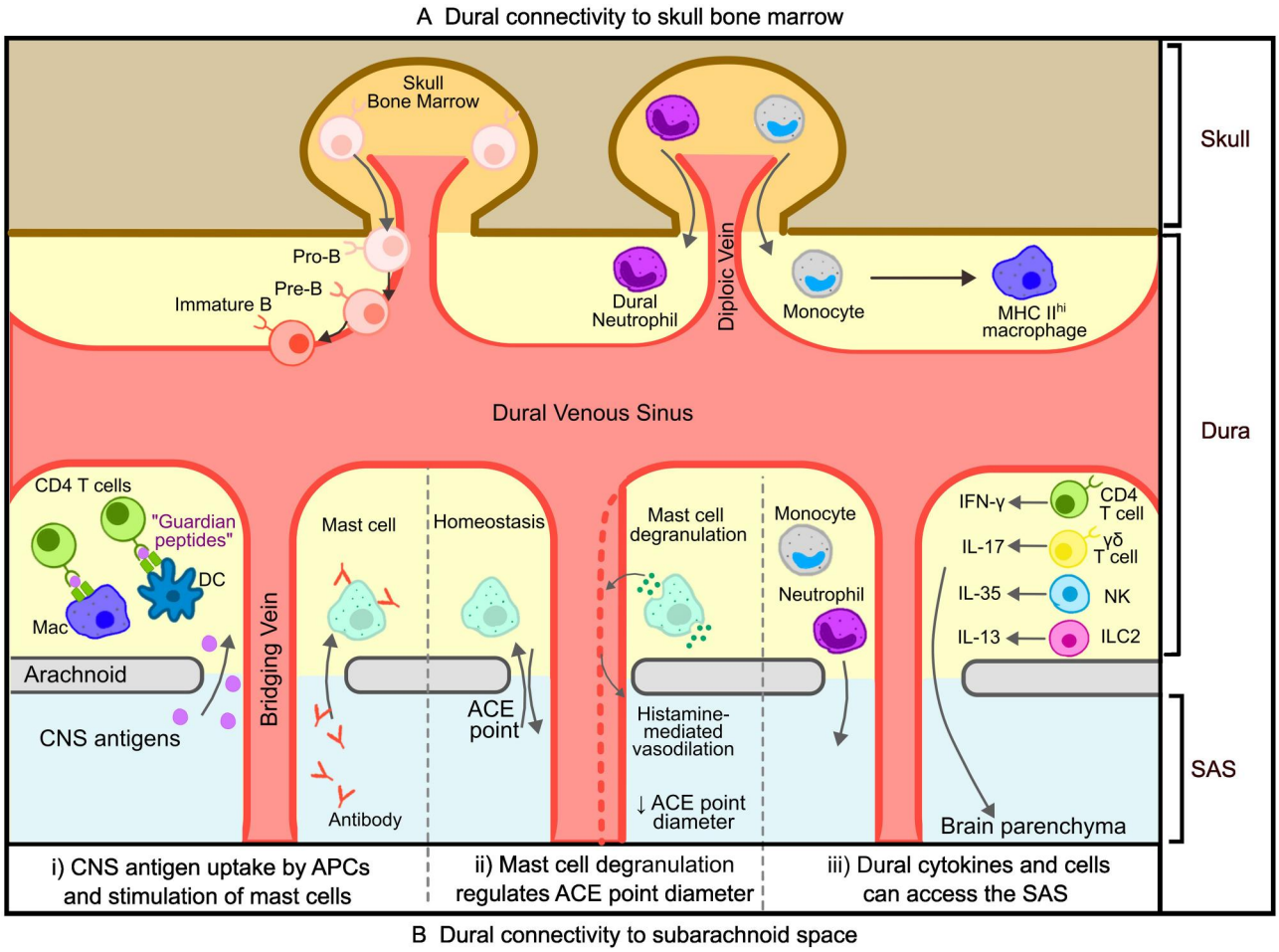


Figure 4. Dural connections with skull bone marrow and subarachnoid space (SAS). (A) Diploic veins drain the skull bone marrow pockets into the venous sinuses, and perivascular channels enable developing B cells, neutrophils, and monocytes to enter the dura, the latter forming MHC II^{hi} dural macrophages. (B) Dural connections to the CSF and leptomeninges via ACE points. (i) Antigens from the CNS, including "guardian peptides" internalized by dural APCs and presented to CD4 T cells. Dural mast cells also shown to bind intracisternal administered antibodies. (ii) Mast cell degranulation leads to histamine-mediated vasodilation of bridging veins and closure of ACE points. (iii) ACE points allow dural cells and their cytokines to access the SAS.

connections between the dura and subarachnoid space, challenging the traditional view of the arachnoid barrier as impermeable. Using single-nucleus RNA sequencing to profile leptomeningeal stromal cells, transgenic mouse models for structural visualization, and ultrastructural imaging, the authors demonstrated that bridging veins create discontinuities in the arachnoid barrier at ACE points.[52] These sites permit bidirectional flow of CSF and small molecules. Indeed, tracers injected into the cisterna magna accumulated at key ACE point "hotspots," one of which was at the junction where the rostral rhinal veins meet the superior sagittal sinus, near the rostral-rhinal DALT. Crucially, ACE points were also visualized in healthy humans via gadolinium-enhanced magnetic resonance imaging, confirming their translational relevance.[52] Passage of molecules through ACE point connections is influenced by the extent of vasodilation of the vessels around which these channels are located. Indeed, dural mast cell degranulation and the release of histamine, with the resulting dilation of bridging veins causing a decrease in the perivascular space that limits the spread of bacteria from the dura to the leptomeninges (Fig. 4Bii).[53]

Together, these studies showed that molecules administered into the CSF could be sampled by dural myeloid cells, but whether dural APCs homeostatically present brain-derived endogenous peptides was unclear. To address this question, Kim et al.[54] assessed the MHC II immunopeptidome using mass spectrometry in mouse brain, dura, and deep and superficial cervical lymph nodes. In homeostasis in C57BL/6 male mice, ~12% of peptides captured from dural APCs were brain derived compared with 2.5% in deep cervical lymph nodes and 0.5% in superficial cervical lymph nodes, with CD11c^{neg}CD11b^{+} macrophages numerically the dominant dural MHC II–expressing cell. In male SJL/J mice, ~30% of dural APC MHC II–loaded peptides were brain derived, together suggesting that there is substantial tonic presentation of CNS antigens in the dura. Enriched among MHC II–loaded antigens were some myelin basic protein–derived peptides (dubbed "guardian" peptides), the presentation of which promoted the expansion of CD4 T cells with regulatory capacity that inhibited inflammation in EAE.[54]

The identification of ACE points as sites of direct communication between the subarachnoid space and dura also provides an explanation as to how dural immune cells subsets can rapidly respond to CNS pathologies. For example, in a model of ischemic stroke, dural DCs decreased at 24 h, with a concomitant increase in DCs in the brain.[55] Furthermore,

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dural mast cells produce IL-6 in the context of stroke, contributing to pathology, demonstrated by intracranial reconstitution of IL-6 knockout mast cells in the meninges of the mast cell–deficient WBB6F1/J-Kit^{W}/Kit$^{W\text{-}v}$ mouse.[56] In EAE, a variety of inflammatory cells rapidly infiltrate the dura mater prior to the onset of clinical symptoms, including monocytes, neutrophils, and T cells.[57] ILC3s are present in the dura in homeostasis and also increase in number in EAE and produce IL-17 and granulocyte-macrophage colony-stimulating factor to activate neutrophils and support encephalitogenic Th17 cells.[58] In a Parkinsons Disease (PD) model, injection of preformed α-syn fibrils into the striatum of wild type mice led to delayed dural lymphatic drainage, increased infiltration of macrophages in the dura, and an increase in dural proinflammatory cytokines.[59]

A recent study investigated dural lymphoid aggregates/DALT in murine models of neurodegenerative disease, including models overexpressing mutated human Aβ (5xFAD and APP/PS1) and a strain expressing mutated human Tau (K257T/P301S) related to frontotemporal dementia.[26] 5xFAD mice showed an increase in DALT aggregates compared with WT mice in older animals. In APP/PS1 younger male mice, there were also increased aggregates compared with controls, but these decreased in size with age. In models with hyperphosphorylated human tau pathology, there was a decrease in DALT aggregates with increasing age.[26] Overall, these observations suggest that there is active communication between the CSF compartment and the dura and that DALT cell number may be modulated by CNS pathology.

Information transfer to the CNS from the dura

The dura can acquire immunological information from multiple sources and sites, but the existence of ACE points potentially provides a route for dural immune cells to convey immunological context to the brain via cytokine production or even direct movement of cells into the leptomeninges (Fig. 4Biii). Early studies focused on dural CD4 T cell–derived cytokines such as IL-4 and IFN-γ, showing effects on learning and memory and social behavior, respectively.[33,60] A more recent study demonstrated that neutrophil activation could drive dural Th1 IFN-γ secretion, which enhanced GABAergic inhibitory signaling within the prelimbic cortex, blunting behavioral responses to threatening stimuli.[31] Administration of an IFN-γ neutralizing antibody into the cisterna magna resulted in reduced synaptic glutamic acid decarboxylase and gephyrin levels, consistent with decreased GABAergic signalling.[31] Dural NK cells can also produce IFNγ, which regulated TRAIL expression in astrocytes, and LAMP1^{+} TRAIL^{+} astrocytes were involved in limiting CNS inflammation in EAE.[34] In a separate study, dural NK cells were shown to secrete IFN-γ and acetylcholine, and depletion of NK1.1^{+} cells or IFN-γ neutralisation led to changes in anxiety-like behavior or memory, respectively, in mice.[61]

IL-17 secretion from dural γδ T cells has been implicated in regulating short-term memory and anxiety-like behavior.[62,63] Furthermore, in a mouse model of Alzheimer's disease there was an increase in IL-17 producing γδ T cells in the dura and brain in female mice, with administration of an intraventricular IL-17 neutralizing antibody preventing short-term memory and synaptic plasticity deficits.[64] Type 2 innate lymphoid cells (ILC2s) are the most abundant ILC in the dura in homeostasis and respond to spinal cord injury, with adoptive transfer of ILC2s into IL-33R$^{-/-}$ mice leading to improved recovery.[65] Further, dural ILC2s, specifically through IL-13, promote signaling to inhibitory interneurons to induce synapse development and density to promote social behavior in mice.[66]

MAIT cells, innate lymphocytes that are abundant in mucosal sites, have also been identified in the dura, where they localize near venous sinuses. In homeostasis, meningeal MAIT do not express IL/17 and IFN/γ like their mucosal counterparts, but rather display transcriptional programs enriched for antioxidant pathways, including selenium transporters. MAIT cell deficient *Mr1*$^{-/-}$ mice showed an accumulation of reactive oxygen species (ROS) in the leptomeninges, leading to arachnoid cell junction disruption and reduced leptomeningeal barrier integrity, which in turn was associated with hippocampal microgliosis, mild astrogliosis, and impaired cognitive function. These effects were substantially attenuated by administration of the antioxidant glutathione to *Mr1*-deficient mice, specifically implicating MAIT cells in the homeostatic control of meningeal ROS accumulation required for the preservation of leptomeningeal integrity and the protection of the underlying brain parenchyma.[67] MAIT cells were also found to be protective in EAE, promoting amphiregulin-dependent tissue repair.[68]

In addition to cytokine and ROS transit from dura to CSF and leptomeninges, there is evidence that immune cells themselves may utilize ACE points. In EAE, GR1^{+} myeloid cells accumulated around ACE points and monocytes and neutrophils were observed in the leptomeninges, potentially due to decreased expression of chemorepellents in the leptomeninges, promoting immune cells migration from the dura into the subarachnoid space.[52] A recent study from the Mathis lab dissected T regulatory cell heterogeneity in the dura.[69] Using a Foxp3 reporter mouse, they found that Foxp3-positive cells comprised ∼15% of dural CD4 T cells, and identified a Th1-like subset and T follicular regulatory cells (as noted previously in single-cell RNA sequencing profiling of rostral-rhinal DALT).[24] They found that depletion of T regulatory cells in adult mice using intraperitoneal administration of diphtheria toxin in the Foxp3–diphtheria toxin receptor mouse led to an increase in the number of conventional CD4 and CD8 T cells within the dura, increased IFN-γ production by dural CD4 T cells and NK cells, and T cell and NK infiltration into the brain parenchyma, with associated activation of glial cells in the hippocampus and short-term memory impairment.[69] The authors noted a marked increase of T cells in the velum interpositum, a double-layered invagination of the pia mater under the hippocampus, proposing that circulating cells may move into the dura and access the brain via the pial velum interpositum,[69] presumably moving via ACE points to access the leptomeninges.

Dural B cells may also contribute to the production of the immunoregulatory cytokine IL-35, or act as a source of IL-35–secreting B cells that localize to the brain. In the 5xFAD model of Alzheimer's disease, there was an increase in the number of B cells in the dura and frontal cortex in 3-month-old mice, prior to the onset of neuropathology. Depletion of B cells aggravated pathology, with B cell–derived IL-35 inhibiting neuronal BACE1 expression, an amyloidogenic enzyme, thereby reducing Aβ load in the brain.[70] The route by which these B cells access the parenchyma was not investigated in the study, but the parallel changes in dura and brain are consistent with migration from the dura via ACE points.

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This increasing evidence demonstrating connectivity between the dura and underlying leptomeninges and brain make it an important gatekeeping structure that modulates the entry and exit of cells and molecules to and from the CSF. Many open questions remain about the cellular and molecular controllers of this bi-directional trafficking, whether, and how these controllers are altered in CNS diseases, and if they can be manipulated therapeutically, for example, to reduce inflammation.

Conclusion

Altogether, the explosion of meningeal immune research has transformed our view of the dura mater, from that of a passive barrier to a dynamic immunological hub. The recent discovery of DALT and its capacity to support adaptive immune responses has important implications for how immune responses may develop to CNS antigens. The identification of ACE points also highlights how immune cells within the dura can potentially influence processes within the leptomeninges and brain and provide a route for drainage of CNS antigens to dural immune cells. While there are many outstanding questions about the cues governing immune cell localization, whether dural immigrants are limited to gut cells or arise from other organs is yet to be determined. Regardless, a better understanding of dural immunity will be essential for developing targeted therapies that leverage this compartment to prevent or treat CNS disorders.

Author contributions

M.R.C. conceived the review outline. K.N., Q.W., and M.R.C. wrote the manuscript. K.N., Q.W., and N.R. produced the figures.

M.R.C. (Conceptualization [Equal], Writing—original draft [Equal], Writing—review & editing [Equal]), K.N. (Writing—original draft [Equal]), Q.W. (Writing—original draft [Equal]), and N.R. (Visualization [Supporting])

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Conflicts of interest

None declared.

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