JEM Journal of Experimental Medicine

REVIEW

# Immune cells and CNS physiology: Microglia and beyond

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**Recent advances have directed our knowledge of the immune system from a narrative of "self" versus "nonself" to one in which immune function is critical for homeostasis of organs throughout the body. This is also the case with respect to the central nervous system (CNS). CNS immunity exists in a segregated state, with a marked partition occurring between the brain parenchyma and meningeal spaces. While the brain parenchyma is patrolled by perivascular macrophages and microglia, the meningeal spaces are supplied with a diverse immune repertoire. In this review, we posit that such partition allows for neuro–immune crosstalk to be properly tuned. Convention may imply that meningeal immunity is an ominous threat to brain function; however, recent studies have shown that its presence may instead be a steady hand directing the CNS to optimal performance.**

## Introduction

A daily challenge during the lifespan of an organism is the preservation of homeostasis. This includes water and nutrient acquisition, temperature change, physical and psychological stress, infection, cancer, and autoimmune processes. Some 4.5 billion years of evolution have helpfully selected responses to these processes, with resulting organismal diversity to fill ecological niches and plastic organ systems to ensure survival and adaptation.

One way that organisms have adapted to facilitate survival is through the evolution of the immune system, enabling species to both combat and tolerate homeostatic perturbance. While this system is classically viewed as the ultimate defense mechanism against the gamut of "self" versus "nonself" interactions, recent breakthroughs have revealed that the immune system's role is much more diverse than previously thought, encompassing both responses to and maintenance of homeostasis. The immune system's functions in maintaining homeostasis, other than resolution of infection, include responding to sterile injury by recognizing "danger" signals (Matzinger, 1994; Pradeu and Cooper, 2012), engaging in immunosurveillance of cancer (Vesely et al., 2011), and facilitating wound resolution and regrowth of tissue (Sonnemann and Bement, 2011; Gause et al., 2013; Hamidzadeh et al., 2017).

Recent imaging techniques and genetic models have also defined organ-specific support roles for the immune system, which ensure proper organ function. These roles include the promotion of immune tolerance and gut peristalsis via crosstalk between muscularis macrophages and enteric neurons in the gut (Muller et al., 2014; Gabanyi et al., 2016), the prevention by T reg cells of tissue damage in the lungs (Arpaia et al., 2015) and in skeletal muscle (Villalta et al., 2014), and the control of thermogenesis in adipose tissues in response to cold (Nguyen et al., 2011; Qiu et al., 2014; Odegaard et al., 2016). Given the ability of the immune system to respond appropriately to a variety of infectious and sterile insults, it makes sense to expect that it would also be poised to respond to such organ stresses, thereby ensuring proper function. While the examples concerned above directly apply to organs of the periphery, immune regulation of organ physiology is also a critical factor of homeostasis within the central nervous system (CNS).

Despite the novelty of immune control of physiology in the periphery, neuroimmunologists have studied this type of immune regulation in the CNS for many years. While earlier studies were primarily concerned with interactions between the immune system and the brain in the domain of pathology (Payan et al., 1986; Kornek et al., 2000), the research in recent decades has placed growing emphasis on physiological interactions of immunity and the brain (Kipnis et al., 2008; Schwartz and Kipnis, 2011; Kettenmann et al., 2013; Deczjowska et al., 2018).

A unique feature of CNS–immune system physiology, however, is that the entire region of the brain parenchyma is excluded from the peripheral immune system and that baseline parenchymal immunity is instead mediated by microglia, the

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https://doi.org/10.1084/jem.20180199

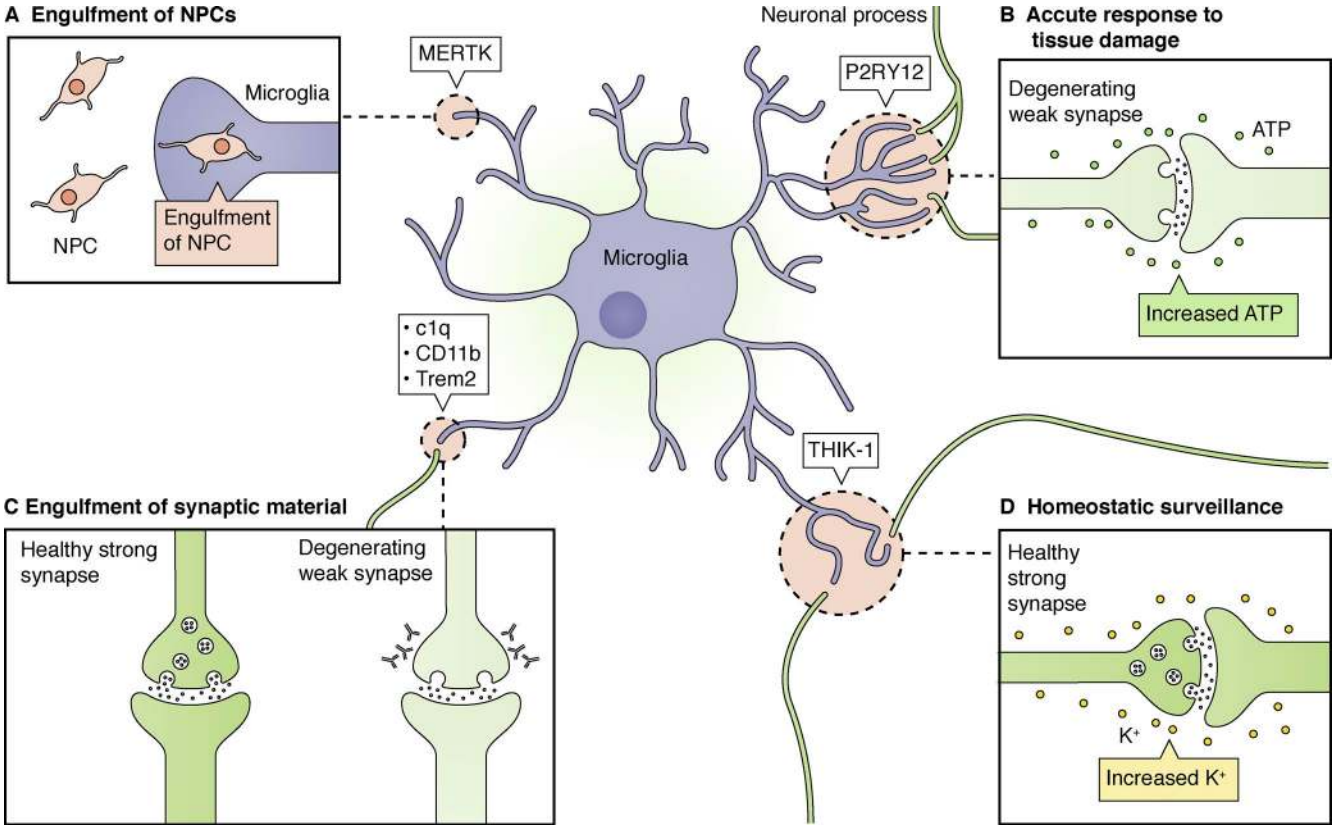


Figure 1. **Homeostatic functions of microglia. (A)** At various time points of neurogenesis, microglia display a critical role in regulating the number of neural progenitors through phagocytosis (Marín-Teva et al., 2004; Squarzoni et al., 2014; Ribeiro Xavier et al., 2015). **(B)** Microglia respond acutely to CNS damage by sensing ATP through P2RY12 signaling (Davalos et al., 2005). **(C)** Engulfment of synaptic material in development and disease is regulated by complement-mediated recognition (Hughes, 2012; Kettenmann et al., 2013). **(D)** Homeostatic surveillance by microglial processes is regulated by the potassium channel THIK-1 (Madry et al., 2018).

tissue-resident macrophages of the brain. In contrast, the meningeal borders of the CNS are not excluded from circulation by peripheral immune cells. Importantly, this segregation seems to be critical for proper functioning of the CNS, as the presence of adaptive immunity within the brain parenchyma is indicative of chronic brain infection or autoimmunity. Still, several lines of evidence demonstrate the importance of meningeal immune cells and their derived cytokines in brain function from worms to mammals (Kipnis, 2016; Rankin and Artis, 2018). Collectively, this points to a fragile balance of homeostatic support by adaptive immune activity in the CNS, which will be discussed later.

In addition to being the major site for immune surveillance, the meninges also house lymphatic vessels capable of draining soluble molecules derived from the brain parenchyma and cerebrospinal fluid (Aspelund et al., 2015; Louveau et al., 2015, 2018; Antila et al., 2017; Da Mesquita et al., 2018). How meningeal lymphatics impact both nervous and immune functions in the CNS is an important question in the field of neuroimmunology, and attempts to resolve it have yielded some crucial insights into processes of both CNS homeostasis and disease.

The apparent paradox of CNS–immune segregation and the unique interface that the meninges provide between these two systems will be the focus of this review, in which we scrutinize the key roles of parenchymal microglia and meningeal adaptive immunity in coordinating this aspect of CNS–immune system physiology.

## Mechanisms of microglial colonization

In recent years, a large focus of research in neuroimmunology has been centered on the resident immune population of the brain parenchyma, microglia. As the brain's tissue-resident macrophage, microglia exhibit a myriad of functions including, but not limited to, surveillance of baseline neuronal activity, rapid response to tissue damage, and developmental engulfment of neural progenitors and synaptic material (Fig. 1). These functions have proven to be key features of microglial biology and are reviewed from a variety of perspectives (Hughes, 2012; Cronk and Kipnis, 2013; Colonna and Butovsky, 2017; Salter and Stevens, 2017).

Microglia, like many other tissue-resident macrophages, arise from immune progenitors in the fetal yolk sac (Ginhoux et al., 2010, 2013). Unlike most other tissue-resident macrophages, however, microglia receive no added contribution to their population from either the fetal liver–derived or the peripheral monocyte–derived macrophage pool (Ajami et al., 2007; Hoeffel et al., 2015). Entering the CNS as early as embryonic day 9.5, microglia are present in the CNS much earlier than astrocytes and even before the onset of true cortical neurogenesis, which starts on approximately embryonic day 12 (Miller and Gauthier, 2007).

The identity of the signals that recruit microglial progenitors into the developing mammalian brain has been a controversial subject, though maintenance of the microglial population has

been ascribed to CSF 1 receptor (M-CSF-R) and its ligand, IL-34, since either blockade of M-CSF-R or deletion of IL-34 results in a lack of microglia (Wang et al., 2012; Squarzoni et al., 2014; Ulland et al., 2015).

Surprisingly, chemokines were shown to have a minimal role in terms of colonization of murine microglia with fractalkine and its receptor CX3CR1, dispensable for the entry of microglia into the developing brain (Squarzoni et al., 2014). This was also reported in a study that showed that chemokine–receptor signaling in total is of minimal importance for microglial brain entry, as normal numbers of microglia are displayed within the developing brain of mice deficient in CCR1, CCR2, CXCR3, or Tyrobp (DAP12; Kierdorf et al., 2013).

A mechanism of microglial brain entry was shown to occur, however, in the developing zebrafish, where death of neural progenitor cells (NPCs) and the subsequent release of purinergic signals such as ATP were found to be necessary for proper microglial infiltration and consequent engulfment of NPCs (Casano et al., 2016). Thus, ATP release may be a critical mediator of microglial entry into the brain as ATP sensing is the key mediator in extension of the microglial process and migration to focal sites of injury in adulthood (Davalos et al., 2005). Interestingly, P2Y12 receptor–deficient mice exhibit the same number of microglia as their wild-type counterparts (Haynes et al., 2006), implying that there may multiple mechanisms for microglial brain colonization.

### Microglia as a baseline immune sentinel

Microglia and perivascular macrophages are the only resident immune cells of the brain parenchyma (Goldmann et al., 2016). Microglia, while true tissue-resident macrophages, are in fact unique in terms of their transcriptional program when compared with other tissue-resident macrophages or brain-engrafting monocytes (Gautier et al., 2012; Butovsky et al., 2014; Gosselin et al., 2014; Cronk et al., 2018). Various disease contexts may alter this baseline identity, both in terms of transcriptional profile (Keren-Shaul et al., 2017) and surface markers (Ajami et al., 2018; Mrdjen et al., 2018).

We and others have recently shown that brain environment is critical in acquisition of a unique microglia signature, although engraftment itself is insufficient, with microglia origin playing an important role in transcriptional and functional identity (Bennett et al., 2018; Cronk et al., 2018). Brain-engrafted macrophages derived from peripheral monocytes exhibited dramatic differences compared with microglia which included altered morphology, increased speed of process extension in response to injury, and a unique transcriptional program both at baseline and in response to LPS challenge (Cronk et al., 2018). The epigenetic landscape of microglial precursors as opposed to peripheral monocytes are a plausible contributor to this phenotype and is a subject that merits further study.

A prominent feature of microglia in the homeostatic brain is their high level of interaction with neurons. This is strikingly demonstrated by examining the specific signals and receptors that mediate microglia–neuron communication. Specific signals mediating this communication include ATP, potassium, and fractalkine. ATP was shown to mediate the response of microglia to neuronal damage. Laser burns induced while performing two-photon live imaging of the mouse neocortex demonstrated robust movement of microglial processes in the moments following injury (Davalos et al., 2005; Nimmerjahn et al., 2005). Later experiments revealed that this phenotype was a result of high expression of the purinergic receptor P2RY12 (Gautier et al., 2012; Gu et al., 2016). While the ATP–P2RY12 axis is a requirement for microglial responses to acute injury, this interaction is not needed for the high degree of baseline motility of microglial ramified processes, another feature of microglia but not of other tissue-resident macrophages (Nimmerjahn et al., 2005), but is rather mediated by potassium and its respective channel THIK-1, which is highly expressed on microglia (Madry et al., 2018). Mice deficient in THIK-1 exhibited normal responses to ATP-mediated motility, but deficient baseline motility and surveillance. Further, diminished IL-1β secretion of THIK-1–deficient microglia implies that sensing of potassium by microglia is needed not only for microglial surveillance, but also for their inflammatory capabilities (Madry et al., 2018). Fractalkine receptor is a canonical marker for many tissue-resident macrophages (Davies et al., 2013), including microglia. Fractalkine–microglial interactions in development, homeostasis, and disease are all well documented and discussed more fully in previous reviews (Paolicelli et al., 2014).

### Phagocytic function of microglia during homeostasis

The role of professional phagocyte is central to the function of any tissue-resident macrophage. Phagocytic processes are essential to many organs, including lung, liver, spleen, and gut (Hochreiter-Hufford and Ravichandran, 2013; Arandjelovic and Ravichandran, 2015; Gordon and Plüddemann, 2017). Recent studies have revealed that phagocytosis by tissue-resident macrophages requires certain nonredundant phagocytic receptors in specific organs and that phagocytosis also imprints a tissue-specific macrophage transcriptional identity (A-Gonzalez et al., 2017; Penberthy et al., 2017).

Phagocytic function is also important in microglia, and indeed, much of our insight into baseline phagocytic function has emerged from brain development studies in which microglial phagocytosis was observed to regulate the numbers of neurons via clearance of neuronal precursors. This was first documented in the developing cerebellum, where dying Purkinje cells were found to be surrounded by microglial processes (Marín-Teva et al., 2004). Ex vivo, microglial depletion induced by incubation of cerebellar slices with clodronate-loaded liposomes also resulted in significantly larger numbers of Purkinje cells, suggesting that an additional microglial function is to maintain normal neuronal populations within the cerebellum (Marín-Teva et al., 2004) and possibly in the entire brain. In cerebellar slices incubated with control liposomes nearly all of the microglia were liposome positive, indicating their high capacity for phagocytosis, while astrocytes in the slice cultures were not seen to ingest liposomes (Marín-Teva et al., 2004). Microglia in the developing rat cerebellum were also highly phagocytic of neural precursors (Perez-Pouchoulen et al., 2015), whose engulfment was enriched in the granule cell layer on the third postnatal week. This phenotype was also seen in developing cortex, in which embryonic depletion of microglia yielded an increased number of cortical

interneurons, implying that microglial phagocytosis or activity is necessary for shaping cortical development (Squarzoni et al., 2014). Microglia are also phagocytic under homeostatic conditions in the adult mouse brain, with subventricular zone (SVZ) phagocytosis of neuronal progenitors seen in the rostral migratory stream (RMS) and the olfactory bulb (Ribeiro Xavier et al., 2015). Furthermore, depletion of SVZ and RMS microglia led to a dramatic increase in the number of NPCs reaching the olfactory bulb, suggesting that SVZ microglia contribute to the successful migration of NPCs from the SVZ (Ribeiro Xavier et al., 2015). A receptor-driven mechanism for this process has recently been assigned to MERTK as the SVZ and RMS of *Mertk*$^{-/-}$ mice were filled with NPC corpses, implying that this receptor which is highly expressed on many tissue-resident macrophages is essential for microglial clearance of NPCs during homeostasis (Fourgeaud et al., 2016).

Importantly, homeostatic engulfment by microglia is not limited to NPCs, as they also engulf developing neuronal processes. This is best documented by the phagocytosis of neuronal material in the mouse visual system during critical periods. Initially, cortical-projecting thalamic relay neurons receive input from the eye by up to 10 individual neurons, which are dramatically reduced to one or two by activity-dependent stimulation that starts before eye opening and continues to postnatal day 30 (P30; Hooks and Chen, 2006). Further studies showed that the complement system, specifically C1q, plays a critical role in this neurodevelopment (Stevens et al., 2007). C1q tagging of retinogeniculate neuronal material was found to lead to clearance by microglia in a process that is also dependent on C1q, C3, and CR3 (CD11b; Schafer et al., 2012). Schafer et al. (2012) also showed that a lack of neuronal activity can drive microglial engulfment of material. Specifically, tetrodotoxin-induced dampening of neuronal activity in the eye increases engulfment of weakened presynaptic inputs relative to controls, while increased neuronal activity in the eye leads to a decrease in engulfed material (Schafer et al., 2012). It has not, however, been directly measured whether neuronal activity controls complement deposition by retinal ganglion cells.

Developmental phagocytic activity was also recently linked to the microglial receptor TREM2, with *Trem2*$^{-/-}$ mice exhibiting increased synaptic density and neuronal activity in the hippocampus that resulted in poor learning and social behavior later in life (Filipello et al., 2018). Thus, the phagocytic activity of macrophages can be directly linked to brain function in adulthood. It was shown, however, that astrocytes are phagocytic during neurodevelopment as well, consuming 5–10 times as much synaptic material as microglia, thus indicating that, at least in neurodevelopment, microglia are not the only phagocytes at work (Chung et al., 2013).

### Complement-mediated synapse clearance in parenchymal pathology

In chronic neurodegeneration, dystrophic or degenerating neuronal processes often act as critical drivers of microglial activation. Glial cells then may serve to amplify neuronal dysfunction, often leading to exacerbation of the underlying neuronal pathology or wholesale neuronal death. During this process, glia play active roles in the clearance of neuronal cells, cell processes, or waste products. Surprisingly, the complement system, which in development is critical for removal of unwanted neuronal connections, is also at play in the case of pathology, where microglial removal of synaptic material is robust (Kettenmann et al., 2013; Salter and Stevens, 2017).

This is apparent after injury to the eye or optic nerve, which carries neuronal projections from the retina to distal sites within the brain. In a recent study, our lab showed that optic nerve crush injury led to microglial enfulfment of neuronal debris that surprisingly was not due to cessation of neuronal activity (Norris et al., 2018), as is the case in development. While neuronal activity was not important in regulating engulfment of debris after injury, microglia and complement depostion were required, and microglia-depleted or complement-deficient mice exhibited excess neuronal debris after injury.

While the phagocytosis of amyloid plaques in mouse models of Alzheimer's disease is an expanding topic of basic and translational research (Koenigsknecht and Landreth, 2004; Fiala et al., 2007; Lai and McLaurin, 2012), an emerging body of literature points to the role of complement proteins in the removal of synapses during Alzheimer pathology at times that precede amyloid deposition and cognitive decline.

Complement was first implicated in a recent genome-wide association study of Alzheimer patients, where single-nucleotide polymorphisms in *CR1*, the gene encoding complement receptor 1 (also known as CD35), was strongly associated with Alzheimer's disease (Tosto and Reitz, 2013). The role of complement in the loss of synapses during early stages of disease was also shown with a marked deposition of C1q in the J20 mouse model of Alzheimer's disease at only 3 mo of age, well before plaque formation (Hong et al., 2016). This deposition coincided with synapse loss and microglial engulfment of synaptic terminals that led to neuronal dysfunction and which was blocked by antibody-mediated blockade of C1q (Hong et al., 2016). The same disease-inducing microglial–complement axis was also ascribed to a mouse model of frontotemporal dementia in *Grn*$^{-/-}$ mice. Reduction of complement deposition by crossing these mice with *C1qa*$^{-/-}$ mice led to a complete reversal of synapse loss and aberrant neuronal dysfunction in the ventral thalamus, as well as amelioration of behavior associated with obsessive-compulsive behavior that is characteristic of *Grn*$^{-/-}$ mice (Lui et al., 2016).

A role for complement and immune activation was also implicated in schizophrenia patients, where a genome-wide association study identified the major histocompatibility complex as a region with the strongest genetic link to pathology of this disease (Ripke et al., 2014). Further examination of patients' genetics and postmortem tissues showed that the complement protein C4 was associated with synaptic processes in the hippocampus (Sekar et al., 2016). That complement plays an additional role in the engulfment of synaptic material was shown in lateral geniculate nucleus development, where C4-deficient mice were found to exhibit overlap of presynaptic terminals within the dorsal lateral geniculate nucleus (Sekar et al., 2016).

West Nile virus (WNV) is the most widely distributed arbovirus (a virus delivered by arthropods such as mosquitos or ticks) with a range that includes every continent except Antarctica (Kramer et al., 2008). Patients suffering from acute encephalitis

related to WNV present with fever, headache, and altered mental status. Survivors of WNV often experience persistent memory impairment, speech disorders, or cognitive impairment (Sadek et al., 2010). In such cases the complement pathway, normally an essential participant in host defense in the periphery and in synapse pruning during development, becomes a player in the post-infection cognitive impairment, with microglia and complement both contributing to a loss of hippocampal synapses (Vasek et al., 2016).

The models described above paint a clear picture of microglial phagocytic activity (largely mediated by complement proteins) in the removal of synapses and subsequent alteration of cognition both in development and in disease states (Stephan et al., 2012; Aguzzi et al., 2013; Kettenmann et al., 2013). Despite this, removal of microglia at baseline does not affect cognitive function (Elmore et al., 2014) raising the question that if microglia are such key players in CNS homeostasis, how is it that their removal does not impact cognition? We hypothesize that a complete absence of microglia may in fact be much less of a homeostatic perturbance than having global, or even region-specific, microglial activation. This may be due to the fact that microglia themselves are not agents of change and inflammation, but rather sentinels primed to monitor and quickly respond to homeostatic perturbations by neurons and other glia. Thus, unless there are stimuli to elicit a microglial response, microglial removal will be benign. Furthermore, baseline removal of complement (studied using *C1qa*$^{-/-}$ mice) causes no change in cognitive ability until advanced age, at which time microglia presumably engage in complement-mediated synapse alteration (Stephan et al., 2013). It thus appears that it is only if microglia are removed during a period when they are perturbed by neuronal dysfunction or engaged in physiological synapse clearance (Han et al., 2017) that their critical function will come to light as at baseline microglia are quiescent watchmen primed for action and not per se responsible for the direct maintenance of CNS homeostasis.

In contrast to removal of microglia at baseline, alteration of meningeal adaptive immunity (via genetic or antibody-mediated depletion of T cells, for example) is sufficient to impair cognitive function. It thus seems that adaptive immune function is an important requirement for baseline cognition, whereas microglia are largely bystanders that closely monitor neuronal function and act responsively only in their proper context.

### Meningeal adaptive immunity and its effect on cognitive processes

The main focus on regulation of cognitive processes by adaptive immunity has been centered on the role of cytokine-secreting CD4 T cells (Fig. 2). In brief, their role largely centers on trafficking to meningeal spaces where cytokine release has been shown to modulate the inflammatory milieu and even neuronal activity directly, which results in profound modification to a variety of cognitive functions including learning and social behaviors (Gadani et al., 2012; Kipnis, 2016; Filiano et al., 2017).

The first instance of T cell modification of neural function was shown some 20 years ago, where transfer of CNS-specific autoreactive T cells into CNS crush-injured rats was found to result in a marked increase in neuronal survival (Moalem et al., 1999). Later studies revealed that T cells could respond to injury independently of T cell receptor specificity, relying instead on their recognition of danger-associated molecular patterns (Walsh et al., 2015). The presence of T cells and their secretion of cytokines in response to damage is not limited, however, to a neuroprotective role.

In 2004, it was shown that T cell deficiency leads to impaired learning and memory, as assessed by the performance of T cell–deficient mice in a Morris water maze (MWM) test, where replenishment of T cells sufficed to improve performance (Kipnis et al., 2004). On the other hand, whereas B cells are abundantly present in the mouse meninges, contributing to early oligodendrocyte development in embryogenesis (Tanabe and Yamashita, 2018), their contribution to cognition is minimal and no learning impairment is observed in μMT (B cell-deficient) mice (Radjavi et al., 2014).

T cell trafficking from the periphery to the meningeal compartment is also essential for learning and memory, as shown by the impaired MWM behavior of mice with pharmacological blockade of meningeal entry (Derecki et al., 2010). Specifically, it was shown that anti-VLA4 treatment was sufficient to impair performance inthe MWM, to a similar degree as in T cell–deficient animals. This implies that T cell trafficking to meningeal spaces is required for optimal cognitive performance. That study also documented a critical role for IL-4 in learning and memory, with rescue of cognitively impaired *IL4*$^{-/-}$ mice achieved by passive transfer of wild-type but not of *IL4*$^{-/-}$ T cells, suggesting that meningeal T cell expression of IL-4 was critical to performance in the MWM. IL-4 was also shown to mediate its effect across meningeal borders to induce astrocytic production of brain-derived neurotrophic factor (Derecki et al., 2010), as well as to induce alternative activation of meningeal macrophages which, when injected into T cell–deficient mice, are also capable of boosting cognition (Derecki et al., 2011). These results have been recently confirmed and further extended to IL-13 (Brombacher et al., 2017).

The control of behavior by T cell–derived cytokines is not limited to the IL-4 signaling axis, as a role in social behaviors was also recently shown by T cell–derived interferon gamma (IFN-γ). T cell–deficient and *Ifng*$^{-/-}$ mice exhibited social behavioral deficits, with repopulation with wild-type T cells, but not *Ifng*$^{-/-}$ T cells, sufficient to restore normal social behavior (Filiano et al., 2016). Surprisingly, the effect of IFN-γ on social behavior was mediated by direct signaling of IFN-γ to receptors on cortical interneurons. IFN-γ signaling on inhibitory neurons resulted in regulation of GABA production and thus regulation of the circuit they control (Filiano et al., 2016). These findings could have profound implications for patients with autism spectrum disorders, who exhibit both social behavioral deficits and neuronal hyperconnectivity. Certain autism spectrum disorder patients might thus be amenable to T cell–based treatments, thereby circumventing the need for invasive brain therapy. Also notable in the above experiments was the observation that there were no social behavioral changes in the *Il4*$^{-/-}$ mice, implying that specific T cell–produced cytokines mediate different aspects of brain function (Filiano et al., 2016).

Given their profound effects on cognitive and social behaviors, it would thus make sense that T cells should be relegated to

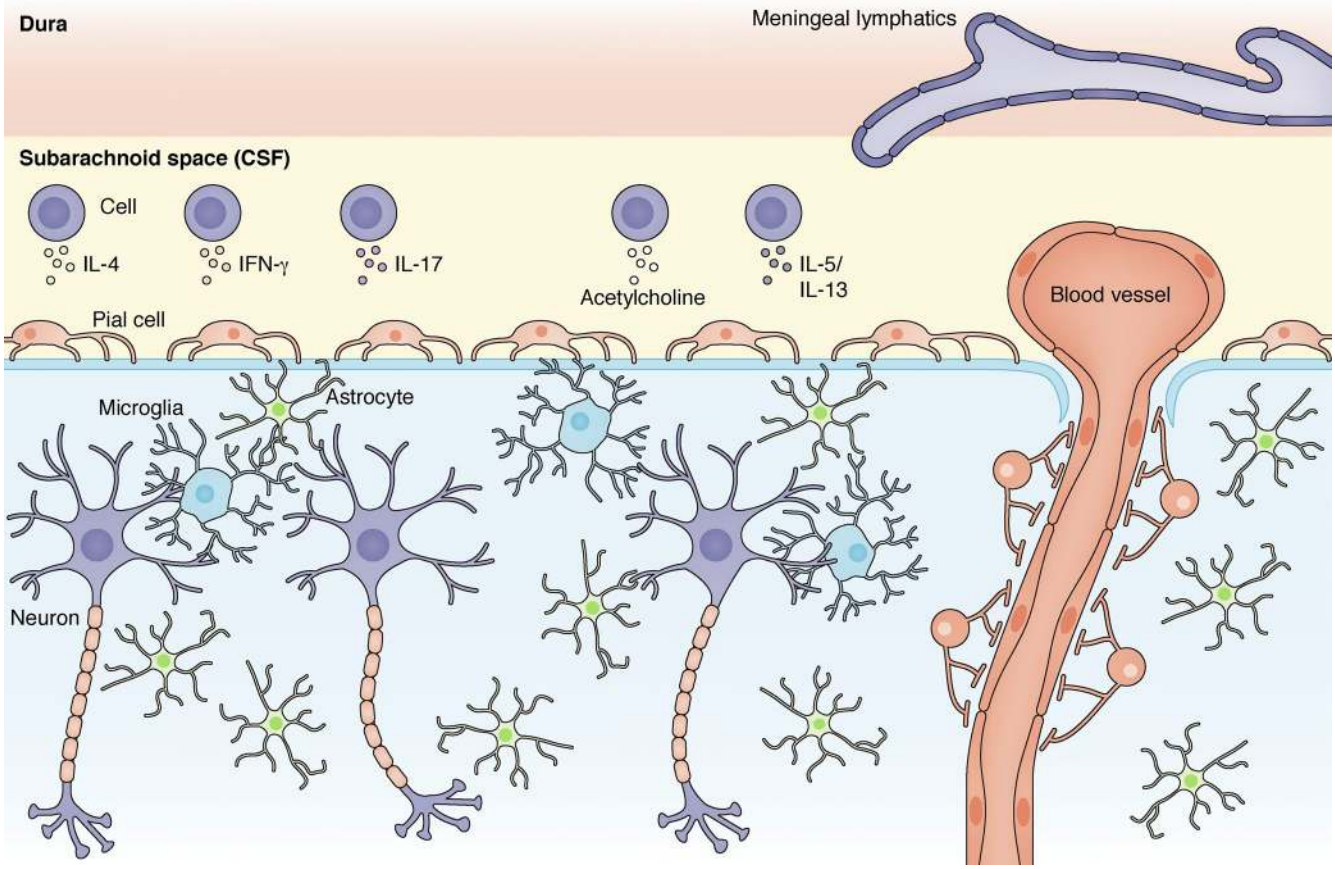


Figure 2. **Meningeal immune-derived cytokines regulate CNS function.** Recent publications have documented roles for the CD4 T cell–derived cytokines IL-4 (Derecki et al., 2010), IFN-γ (Filiano et al., 2016), and IL-17 (Choi et al., 2016) in brain function. T cell–derived ACh has been shown to play a profound role in suppressing autoimmune processes (Chavan et al., 2017) and regulation of blood pressure (Olofsson et al., 2016) while its role in meningeal immunity has not been investigated. ILC2-derived IL-5 and IL-13 is critical for host defense of pathogens in both gut and lung (Cardoso et al., 2017; Klose et al., 2017). While ILC2s are prevalent in the meninges (Gadani et al., 2017), the role of ILC2-derived cytokines in CNS function is unknown.

border regions of the CNS, where the potency of their cytokines could be prevented or at least confined from interacting directly with neurons or glial cells. Further experiments, possibly with tonic release or conditional overexpression of cytokines, may detail the importance of tuning T cell responses in the CNS with respect to delivery of cytokines and T cell localization. The roles of meningeal immunity on brain function have also been recently reviewed elsewhere (Kipnis, 2016; Filiano et al., 2017).

Aberrant T cell function and cytokine production has been shown to have an adverse outcome during maternal immune activation, with T cell–derived IL-17 directly affecting brain development, yielding cortical malformations and altered social behaviors (Choi et al., 2016; Shin Yim et al., 2017). Traditionally viewed as a disease-inducing cell in CNS pathologies (Steinman, 2007; Croxford et al., 2015), IL-17 producing T cells may now need to be reconsidered as inducers of dysregulated CNS development.

Drivers of IL-17 producing T cells include the canonical stimulation paradigm of cytokines including IL-6, TGF-β, and IL-23 (McGeachy and Cua, 2008; Korn et al., 2009). The microbiota has also been shown to be an environmental driver of IL-17 producing T cells, with segmented filamentous bacteria necessary for Th17 cell induction (Ivanov et al., 2009). In the CNS, the microbiota directly affects microglial maturation and function (Erny et al., 2015) and CNS responses to autoimmunity (Rothhammer et al., 2016, 2018). While the microbiome has been known to be a key driver of maternal-immune activation (Hsiao et al., 2013), recently the IL-17–driven pathology seen in maternal immune activation was shown to be dependent on microbiota composition, indicating a direct pathway of environmental factors that can affect brain development through T cell–derived cytokines (Kim et al., 2017; Lammert et al., 2018).

Whether meningeal T cell–derived IL-17 could have a similar effect on cognitive dysfunction outside of embryonic development remains to be seen. Furthermore, IL-17 may have an evolutionarily conserved function, as this cytokine reportedly modulates neuronal chemosensation in *Caenorhabditis elegans* (Chen et al., 2017).

These data, combined with the findings that IL-4 boosts learning and memory (Derecki et al., 2010) and that IFN-γ signaling may underpin social behaviors (Filiano et al., 2016), demonstrate that T cell–derived cytokines can have profound effects on neuronal development, connectivity, and function, while also having well-conserved evolutionary roots. These results also shed a new light on neuroimmune interactions, suggesting that the immune system may operate as a "sensory" arm of the brain, capable of detecting peripheral microorganisms and other threats

and informing the brain about them using the combinatorial language of cytokines (Kipnis, 2018), in addition to more direct interactions via the Vagus nerve (Chavan et al., 2017; Pavlov and Tracey, 2017).

### Separation of powers: a possible rationale for meningeal immunity segregation from the parenchyma

The adaptive immune cytokines mentioned above (IL-4, IFN-γ, and IL-17) are all capable of altering neuronal function and behavior. Cytokines known to affect CNS neuronal behavior are not limited to these three, as extensively reviewed elsewhere (Yarlagadda et al., 2009; Gadani et al., 2012; Miller et al., 2013; Rankin and Artis, 2018). Recent studies have also documented cytokine effects on peripheral neurons: enteric neurons control macrophage homeostasis through cytokine–norepinephrine crosstalk (Muller et al., 2014; Gabanyi et al., 2016); IL-5 released from CD4 T cells in the lung induces release of the neurotransmitter vasoactive intestinal peptide (Talbot et al., 2015); and both IL-4 and IL-13 are capable of inducing itch responses when signaling on sensory neurons in the skin (Oetjen et al., 2017).

In addition to cytokines, immune cells can also produce neurotransmitters that exert direct effects on physiology. Notably, IL-4 can drive white adipose tissue macrophages to produce norepinephrine to induce production of beige adipose tissue (Nguyen et al., 2011), and T cells that sense norepinephrine can synthesize acetylcholine (ACh) to dampen immune responses and control blood pressure (Olofsson et al., 2016; Pavlov and Tracey, 2017). Recent reports, however, question the possibility that macrophages may directly produce norepinephrine (Fischer et al., 2017). Despite these conflicting results the question of immune influence on thermogenesis remains an open and exciting topic for future studies (Reitman, 2017).

Neurotransmitter release from neurons affecting immune function has also been a fertile area of neuroimmunological research in recent years. We discuss two examples here: the neuromedin U (NMU)–ILC2 axis in the lung and gut and the norepinephrine–choline acetyltransferase (ChAT) T cell–acetylcholine axis that dampens immune responses while also ensuring blood pressure homeostasis.

In the field of immunology, ILC2 cells (type 2 innate lymphoid cells) are emerging as a well-documented cell type that plays a critical role in immune responses at barrier tissues in a variety of contexts (Spits and Cupedo, 2012; Licona-Limón et al., 2013; Tait Wojno and Artis, 2016; Rankin and Artis, 2018). In our laboratory, we recently observed ILC2 cells within the meninges serving a neuroprotective role in the context of spinal cord injury (Gadani et al., 2017). Outstanding questions still remain as to whether meningeal ILC2 cytokine release plays a meaningful role in CNS homeostasis and cognition (Fig. 2).

Understanding what prompts ILC2s to promote either homeostatic or inflammatory functions was boosted when it was recognized that neuronal release of the neuropeptide NMU can synergize with alarmins (also known as danger-associated molecular patterns) to promote ILC2 expansion and transcriptional reprogramming (Wallrapp et al., 2017), as well as to restrict *Nippostrongylus brasiliensis* infection in both the gut and the lung (Cardoso et al., 2017; Klose et al., 2017). It thus seems that besides the classic role of alarmins (Van Dyken et al., 2014) and allergens (Martinez-Gonzalez et al., 2017) in activating ILCs, neuronal activity is also critical for synergizing ILC2 activation and hence for organismal barrier protection. An important finding was that ILC2s are the only immune cells that express the NMU receptor and are in close proximity to NMU-expressing neurons (Klose et al., 2017), again pointing to the presence of both spatial and temporal control of immune responses to neurotransmitters in these barrier tissues. An important caveat in several of these works is a reliance on RAG-deficient animals, deficient in T cell and B cell responses, which are critical for homeostatic function and may be important to the experimental results in question.

With ILC2s poised to respond to CNS perturbations, it seems logical that the ILC2s should be located in meningeal spaces surrounding the brain rather than within the brain parenchyma, since the latter is a rich source both of neurotransmitters (Tareke et al., 2007; Kim et al., 2014) and of the ILC2-activating alarmin IL-33 (Gadani et al., 2015).

In the above sections and in previous reviews (Kipnis et al., 2012; Filiano et al., 2017) we have discussed the essential roles of T cell–derived cytokines as players in both cognitive and social functions and argued that from an evolutionary point of view it would make sense to shield CD4 T cells from neurons to prevent alterations in neuronal activity that might result from aberrant cytokine release. Another likely reason for such segregation are the neurotransmitters produced by CD4 T cells. The knowledge that T cells can secrete neurotransmitters was first acquired when ACh was found to be released from CD4 T cells (Fujii et al., 1995). The idea that CD4 T cells could form a powerful anti-inflammatory "immune reflex" capable of suppressing both immune responses to infection and autoimmunity came initially from an observation that cytokine levels in the intestinal mucosa were reduced in patients who were suffering from inflammatory bowel disease and were also cigarette smokers (Sher et al., 1999). That finding led to the hypothesis that nicotine, and stimulation of ACh receptors, would result in dampening of inflammatory responses. This was indeed demonstrated: administration of ACh to macrophages decreased the production of TNF in vitro, and Vagus nerve stimulation (which results in ACh release) dampened in vivo production of liver and serum TNF in rats exposed to LPS (Borovikova et al., 2000). Further study revealed that the primary producers of ACh in response to Vagus stimulation are ChAT-expressing CD4 T cells that reside in the spleen (Rosas-Ballina et al., 2011). The importance of these cells was confirmed by the observation that the enhanced TNF responses exhibited by T cell–deficient mice could be ameliorated by replenishment of ChAT-sufficient T cells (Rosas-Ballina et al., 2011).

Localization of ChAT$^+$ T cells is not restricted to the spleen; around 1% of circulating peripheral blood T cells are positive for ChAT (Olofsson et al., 2016). Moreover, deletion of ChAT from the T cell compartment leads to systemic increases in blood pressure that could be corrected by infusion of ChAT-sufficient T cells (Olofsson et al., 2016). While the identity of the signals regulating such T cell mediation of blood pressure remains an open question, these data indicate that T cell reception and secretion of neurotransmitter can dramatically alter both homeostatic and inflammatory responses.

### Concluding remarks

Complex organisms have coevolved with viruses, foreign pathogens, and commensal microbial communities, allowing for the formation of immune systems capable of balancing efficient immune responses to pathogens while blunting autoimmunity. Evolutionary pressure has also established specialized organ systems capable of responding rapidly to environmental and internal changes. Emerging evidence that the immune system, independently of its antimicrobial function, plays a crucial role in organ homeostasis provides us a novel concept and lens in the attempt to analyze and understand the immune system (Rankin and Artis, 2018). This applies especially to the brain, which is the master organ responsible for executive function of advanced organisms, innervation of nearly all of the body's organ systems, and speedy modulation of peripheral immune function.

Finally, a major point of this review is the idea that the segregated state which appears to define the existence of the immune system within the CNS should be viewed as a crucial partition, allowing for the neuro–immune crosstalk that exists in the periphery to be muted so as to permit proper neuronal and immunological activity. This enables microglia, which, relative to other macrophages, are uniquely tuned to sense neuronal activity, to perform their subtle interactions in the absence of the adaptive immune system. Furthermore, the vast array of adaptive and innate immune cells occupying the meningeal borders of the CNS should be viewed not as a threat to neurological function, but rather as a restrained ally capable of providing, according to need, the essential neuroimmune communication critical for higher neurological processes.

## Acknowledgments

We would like to thank Shirley Smith for editing the manuscript and Anita Impagliazzo for the artwork. We would also like to thank all the members of the Kipnis Laboratory and of the Center for Brain Immunology and Glia for their valuable comments.

This work was supported by grants from the National Institutes of Health/National Institute on Aging (NS096967 and AG034113) and from the Cure Alzheimer's Fund.

J. Kipnis is an Advisor to PureTech Health/Ariya.

G. Norris and J. Kipnis wrote, critically reviewed, and edited the manuscript. All authors reviewed the manuscript before submission.

Submitted: 8 June 2018
Revised: 15 August 2018
Accepted: 13 November 2018

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