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REVIEW

Central Nervous System: (Immunological) Ivory Tower or Not?

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The view of the nervous system being the victim of destructive inflammation during autoimmunity, degeneration, or injury has been rapidly changing. Recent studies are supporting the idea that the immune system provides support for the nervous system at various levels. Though cell patrolling through the nervous system parenchyma is limited compared with other tissues, immune cell presence within the central nervous system (CNS; microglia), as well as around it (in the meningeal spaces and choroid plexus) has been shown to be important for brain tissue maintenance and function. This review primarily explores recent findings concerning neuroimmune interactions and their mechanisms under homeostatic conditions.
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INTRODUCTION

The immune system, although long known for its essential function in the organism's defense against pathogens, has recently also become appreciated as indispensable for tissue maintenance. In addition to constant patrolling by circulating immune cells, every organ, including the brain, benefits from a dedicated resident immune system. Under pathological conditions, both the tissue-resident and the peripheral immunity react rapidly to eliminate the threat and facilitate tissue recovery. The central nervous system (CNS) does not seem to be much different in this regard, despite it long being regarded as an 'ivory tower,' immune-privileged organ. Under physiological conditions, although immune access to the CNS is indeed tightly regulated, the system nevertheless derives essential benefit from parenchymal resident microglia, as well as from an immune repertoire in the meninges and choroid plexus. In this review we discuss the different levels of immune support for the CNS and consider how the nervous system is affected by immune system function in health and disease.

THE BRAIN-RESIDENT IMMUNE SYSTEM

The parenchymal tissue of the CNS contains a limited immune repertoire, composed mainly of resident microglia and perivascular macrophages (although the perivascular space is external to the parenchyma, leaving microglia as the main true immune cell within this part of the CNS) (Figure 1). In the course of embryonic development, the brain is seeded by microglia derived from primitive yolk-sac macrophages (Ginhoux *et al,* 2010; Gomez Perdiguero *et al,* 2015; Sheng *et al*, 2015). During normal postembryonic homeostasis the microglia proliferate within the parenchyma, with no infiltration from the periphery (Ajami *et al*, 2011; Gomez Perdiguero *et al,* 2015; Mildner *et al,* 2007). Although the presence and many macroscopic/histological features of microglia have been known for almost a century (Kettenmann *et al*, 2011), understanding their full range of functions has proved to be challenging. Microglia were first described by del Rio Hortega, who went on to advance the idea that microglia in the CNS behave like microphages in other sites of the body (Kettenmann *et al,* 2011). Modern RNA-seq analyses show that the microglial transcriptome shares homology with tissue-resident macrophages (Gautier *et al,* 2012) while also exhibiting their unique genetic signature. For example, microglia respond rapidly during infection and injury, adopting the characteristic amoeboid morphology (Davalos *et al,* 2005; Roth *et al,* 2014). When this happens, microglia increase their migratory and phagocytic programs (Fourgeaud *et al,* 2016; Roth *et al,* 2014) and become phenotypically indistinguishable from macrophages (Mildner *et al,* 2007; Yamasaki *et al,* 2014).

Less clear are the roles of microglia in the absence of infectious or injury stimuli. With the advancement of *in vivo* imaging techniques, the scientific community began to appreciate the dynamic nature of microglia during their resting steady state (Davalos *et al,* 2005; Nimmerjahn *et al*, 2005;

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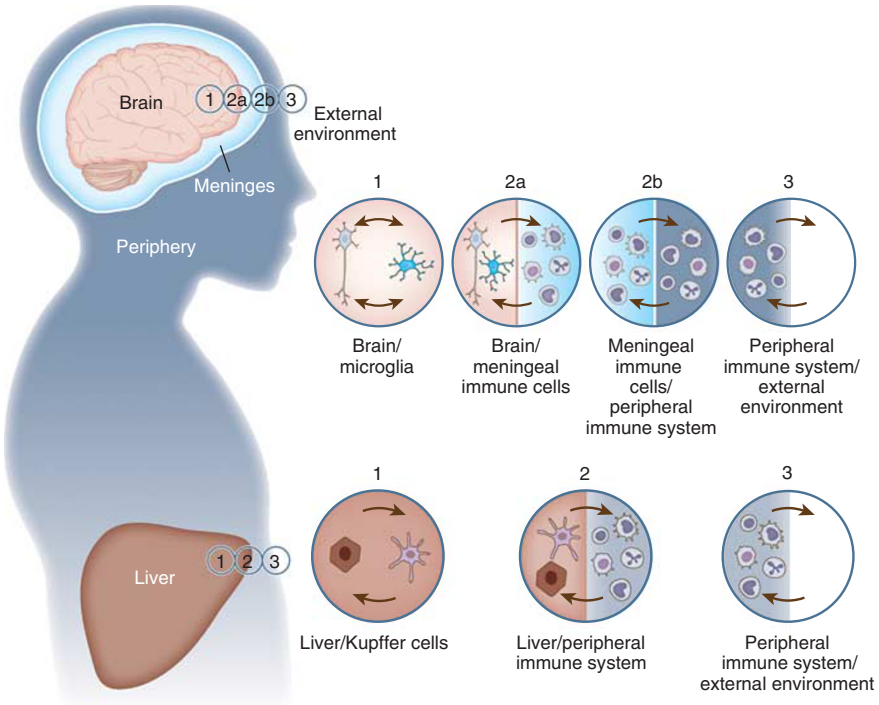

Figure 1. Layers of immune surveillance of the central nervous system (*vs* peripheral organs). The nervous system has long been viewed as isolated from the immune system because of the lack of circulating immune cell infiltration during homeostatic conditions. However, we have recently begun to appreciate that the nervous system benefits from extensive immune support, as well as extensive regulatory mechanisms. The immune presence in the parenchyma (constituted by microglia) is limited, with compartmentalization of a full complement of immune cells in the meninges (and partial in the choroid plexus). Responses from the peripheral immunity translate into immune responses in the meninges and choroid plexus that may then be relayed, in an attenuated manner, to the parenchyma. Such layering allows for protection of the CNS from destructive inflammation (which can be devastating for a bone-enclosed organ sensitive to mechanical stimuli) while still being able to receive, and thus respond to, environmental stimuli. Peripheral organs (exemplified here by the liver) also benefit from specialized tissue-resident immune cells (ie, Kupffer cells in the liver). However, most organs do not benefit from the extra layers of checkpoint (such as meninges in the CNS) for entry of immune cells, allowing them to readily infiltrate directly from the circulation.

Tremblay *et al*, 2010; Wake *et al*, 2009). These cells constantly sample their environment by extending and retracting their processes, and can be observed making contacts with synaptic formations (Paolicelli *et al*, 2011; Tremblay *et al*, 2010; Wake *et al*, 2009). The synaptic contacts appear to be mediated by soluble factors such as ATP and soluble fractalkine, whose release can be mediated by neuronal activity (Dissing-Olesen *et al*, 2014; Eyo *et al*, 2014; Fontainhas *et al*, 2011; Haynes *et al*, 2006; Hoshiko *et al*, 2012; Li *et al*, 2012; Paolicelli *et al*, 2011; Sipe *et al*, 2016). Both raised and lowered neuronal activity seems to trigger synaptic contacts by microglia, although the microglial behavior subsequent to such contact may be different in each case. Glutamate stimulation of either NMDA or AMPA receptors, as well as evoked circuit activity, can drive the release of ATP, inducing elongation of microglial processes via activation of the P2Y12 purinergic receptors on microglia (Dissing-Olesen *et al*, 2014; Eyo *et al*, 2014; Fontainhas *et al*, 2011; Haynes *et al*, 2006; Li *et al*, 2012). The functions of microglial contacts under these circumstances are largely unknown. In a seizure model, loss of signaling through P2Y12 prevents activity-driven extension of microglia and leads to exacerbated seizure severity (Eyo *et al*, 2014), indicating that microglia might play a role in glutamate buffering during intense neuronal activity. On the other hand, decreased neuronal activity, for example by sensory deprivation or inhibition of excitatory signaling, can also increase synaptic contacts by microglia in an ATP-dependent manner (Sipe *et al*, 2016; Tremblay *et al*, 2010). In such cases, the decrease in neuronal activity causes extension of processes but arrest of microglial motility, leading ultimately to an increased microglial intake of synaptic elements (Sipe *et al*, 2016; Tremblay *et al*, 2010).

Synaptic pruning by microglia is important for both normal development and maintenance of homeostasis in adulthood. Upon extension of microglial processes, microglial receptors such as CX3CR1, CR3, CD200R, or TREM2/DAP12 may recognize ligands on the neuronal membrane (Hoshiko *et al*, 2012; Paolicelli *et al*, 2011; Poliani *et al*, 2015; Schafer *et al*, 2012). Perhaps the oldest documented interaction is that between fractalkine (on neurons) and CX3CR1 (on microglia). Mice deficient in CX3CR1 signaling exhibit deficits in the numbers of microglia during development, as well as decreased synaptic pruning (Paolicelli *et al*, 2011). Although the microglia in these mice reach normal numbers in adulthood, they appear to have an exuberant production of inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) (Cardona *et al*, 2006; Cho *et al*, 2011; Dudley *et al*, 2002). Moreover, the mice maintain deficits in synaptic maturation (Hoshiko *et al*, 2012) and

function (Dudley *et al,* 2002; Zhang *et al,* 2014) that translate behaviorally into cognitive and social impairments (Cho *et al,* 2011; Dudley *et al,* 2002; Zhang *et al,* 2014). It is important to note that although many of these effects may be a result of deficient synaptic pruning, they can also be ascribed to a microglial effect on neuronal circuit activity via other mechanisms in response to soluble CX3CL1 (Ragozzino *et al,* 2006).

A more recently described pathway for microglial pruning is the complement system (Stevens *et al,* 2007), in which weaker synaptic inputs on developing neurons are decorated with C1q and C3 molecules capable of engaging CR3 receptors on microglia for targeted elimination (Schafer *et al,* 2012; Stevens *et al,* 2007). Classical and nonclassical signaling of complement components is also active in adulthood and aging, but its implications for microglia are unknown. In aged mice, for example, C1q is increased both at synapses and on microglia, and C1q- and C3-knockout mice are protected from cognitive impairments (Shi *et al,* 2015; Stephan *et al,* 2013). Increased complement decoration at synapses can be induced by oligomeric Aβ, and is also observed in mouse models of Alzheimer's disease. In this context, it appears that there is excessive microglial engulfment of synapses in a CR3-dependent manner (Hong *et al,* 2016).

Although the evidence described above points to important roles for microglia in wiring of the brain, more recent efforts have been directed toward understanding the roles of microglia specifically in adulthood. Studies have employed both genetic (*CX3CR1*$^{CreER/+}$*:R26*$^{iDTR/+}$) and pharmacological approaches (CSF1 antagonists such as *PLX3397*) to cause extensive microglial death in the adult or aged CNS (Elmore *et al,* 2014; Parkhurst *et al,* 2013). The short-term effects of such drastic approaches appear to be subtle, expressed as mild cognitive impairments (Parkhurst *et al,* 2013) or with no behavioral effects at all (Elmore *et al,* 2014). Ablation of microglia does not induce neuronal loss, but longer-term ablation can cause synaptic degradation (Parkhurst *et al,* 2013; Spangenberg *et al,* 2016; Wang *et al,* 2016). Intriguingly, in mouse models of Alzheimer's disease with its hallmark microglial activation and proliferation, the effects of microglial ablation are beneficial (Hong *et al,* 2016; Olmos-Alonso *et al,* 2016; Spangenberg *et al,* 2016). In particular, loss of microglia prevents spine loss and cognitive impairments, but has no effect on Aβ levels.

Taken together, recent evidence points to discrete roles for microglia in circuit wiring, aiding neuronal function, and maintaining CNS homeostasis. However, under conditions of neuronal degradation and low-grade inflammation (such as cognitive decline and aging), microglia appear to accelerate both the functional loss of neurons and the cognitive decline.

CHOROID PLEXUS: AN ENTRY POINT FOR PATROLLING IMMUNE CELLS?

The main function of the choroid plexus, an epithelial tissue located within the ventricles of the brain, is filtration of the blood to yield the cell-free low-protein cerebrospinal fluid (CSF). Although the cell count in the CSF is low, it is not negligible (1000 – 3000 cells per ml in humans; Kivisakk *et al,* 2003), and an increase in the number is taken as a sign of neuroinflammation (Giunti *et al,* 2003). Immune cells are also found within the choroid plexus epithelium, and during inflammatory events their numbers increase (Giunti *et al,* 2003; Young *et al*, 2011), giving rise to the hypothesis that the choroid plexus is one of the points of immune-cell entry into the CSF. Adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and P-selectin, are expressed in the choroid plexus at baseline, providing a permissive environment for immune-cell infiltration (Baruch *et al,* 2015; Kivisakk *et al,* 2003). The levels of such adhesion molecules, as well as of tight junction components, are dynamically controlled by the cytokine milieu and inflammatory stimuli to regulate the amounts of cell traffic into the CSF (Baruch *et al,* 2015; Kunis *et al,* 2013; Marques *et al,* 2009; Zhang *et al*, 2013). Inflammatory stimuli, such as peripheral infection or autoimmune diseases, are usually 'activators' of the choroid plexus (Marques *et al,* 2007, 2009; Petito and Adkins, 2005; Reboldi *et al,* 2009; Shrestha *et al*, 2014; Young *et al,* 2011; Zhang *et al,* 2013). In contrast, an aging milieu renders the site more quiescent for immune-cell trafficking (Baruch *et al,* 2013, 2015; Mesquita *et al,* 2015).

'Activation' of the choroid plexus usually refers to upregulation of inflammatory cytokines (such as IL-1β, TNFα, and IL-6), as well as upregulation of adhesion molecules and downregulation of tight junction molecules (Marques *et al,* 2007, 2009; Shrestha *et al,* 2014; Young *et al,* 2011). Interestingly, the inflammatory response to peripheral stimuli in the choroid plexus is much weaker than in other organs in the periphery (liver, spleen) and is subjected to tight temporal regulation, usually resolving within 24 h of the stimulus (Marques *et al,* 2009; Shrestha *et al,* 2014). As a result, peripheral stimuli in the choroid plexus normally dictate the entry of only a limited, nonantigen-specific immune-cell infiltrate into the CSF (Petito and Adkins, 2005; Shrestha *et al,* 2014; Young *et al,* 2011). Under autoimmune conditions, however, entry of the infiltrate is more extensive (Giunti *et al,* 2003; Shrestha *et al,* 2014). In addition to the temporal regulation (whose mechanisms are as yet unknown), other mechanisms, such as shedding of syndecans, may limit the extent of the choroid plexus infiltrate (Zhang *et al,* 2013). During autoimmune encephalitis, syndecan is shed from the choroid plexus epithelium into the CSF, where it acts like a sponge to bind released chemokines, thus sequestering them from accumulating lymphocytes (Zhang *et al,* 2013).

More recent work has focused on the role of the choroid plexus as the site for neuroimmune interactions in aging and models of Alzheimer's disease. Lymphocyte levels in CSF samples from aged individuals are decreased, whereas tau protein accumulates and monomeric Aβ decreases (Lueg *et al,* 2015). In a mouse model of Alzheimer's disease, Aβ protein accumulates in the CSF much earlier (after 3 months)

than its deposition is detectable in the brain parenchyma (after 12 months) (Mesquita *et al,* 2015). Moreover, studies in aged mice showed that the cytokine milieu of the choroid plexus is shifted toward a type 2 skew, with increased IL-4 and decreased interferon-γ (IFNγ) levels (Baruch *et al,* 2013; Mesquita *et al,* 2015). At the same time, mice with impaired IFNγ signaling show a decrease in adhesion molecules in the choroid plexus and impaired immune-cell trafficking at this site, indicating a possible role for type 1 signaling in maintaining immune function in the CNS (Kunis *et al,* 2013; Raposo *et al,* 2014). Transient suppression of regulatory T cells in mouse model of Alzheimer's disease resulted in upregulation of adhesion molecules in the choroid plexus, as well as increased lymphocyte recruitment (Baruch *et al,* 2015). These mice also exhibited improved cognitive performance, indicating that increased immune activity at the choroid plexus is beneficial in this model.

Studies have indicated that under pathological conditions the choroid plexus can be an active site for immune trafficking into the CNS, but they do not exclude other routes, such as through the meningeal vasculature (Young *et al,* 2011). A new study, using rats with experimental autoimmune encephalomyelitis (EAE) as a model, indeed points to the meningeal blood vessels as the main site for immune-cell trafficking at specific time points during EAE development (Schlager *et al,* 2016). One possibility is that at certain time points during the inflammatory process, infiltration through the choroid plexus is regulated via specific pathways (such as those mediated by CCR6 or syndecan) (Reboldi *et al,* 2009; Zhang *et al,* 2013). It seems, however, that more thorough characterization of the immune responses in each compartment of the CNS is needed. One question that the field is actively trying to address is whether and how immune cells can infiltrate into the parenchyma once in the CSF. Though CSF washes throughout the brain, it is mostly confined to the ventricles and meningeal spaces. The recently described glymphatic system (Iliff *et al,* 2013; Iliff and Nedergaard, 2013) proposes that CSF can also drain along large arteries and from there into the interstitial space and back in the perivenular space for molecular clearance. Whether cells can also use this route to move from CSF into the parenchyma remains unknown. Alternatively, cells could transverse the pia mater or ventricular lining to enter the parenchyma. Regardless of the route, the cells would have both extracellular matrix and astrocyte barriers to overcome and direct evidence (ie, imaging) for either process is still lacking.

Also missing is knowledge of the homeostatic regulation of cell trafficking through the choroid plexus, as well as a better understanding of the function of immune cells in the CSF. Are they regulated by neuronal activity? Are they needed for immunosurveillance, or perhaps for secretion of tonic levels of cytokines? Do they sample CNS antigens to maintain tolerance? Addressing these questions is made more difficult by the lack of means to inhibit trafficking specifically through the choroid plexus.

MENINGEAL SPACES: IMMUNE SURVEILLANCE AROUND THE BRAIN

The meningeal compartment of the CNS contains a wide repertoire of immune cells within the membranes that surround the parenchymal tissue, rendering this compartment an immunologically competent site (Figure 1) (Bartholomaus *et al,* 2009; Derecki *et al,* 2010; Hatfield and Brown, 2015; Kim *et al*, 2009; Levy *et al*, 2007; Louveau *et al,* 2015; Sayed *et al*, 2010). Studies have shown that under inflammatory conditions the numbers of immune cells in the meningeal compartment can increase, possibly on a larger scale than in the choroid plexus (Bartholomaus *et al,* 2009; Kim *et al,* 2009; Kivisakk *et al,* 2009; Sayed *et al,* 2010; Schlager *et al,* 2016). For example, synchronous extravasion of neutrophil waves was observed in the meninges of murine viral meningitis models (Kim *et al,* 2009). Extensive infiltration in the meninges was also observed in rodents with EAE (Bartholomaus *et al,* 2009; Kivisakk *et al,* 2009; Schlager *et al,* 2016). Recent evidence suggests that such infiltrating autoimmune cells can then invade the parenchyma via the pial membrane (Schlager *et al,* 2016). In addition to the various molecular players that regulate infiltration, meningeal mast cells seem to play an important role in gatekeeping of immune cell infiltration during EAE, as well as in other inflammatory contexts, such as stroke (Arac *et al,* 2014; Christy *et al*, 2013; Sayed *et al,* 2010).

Though much less intensively investigated, meningeal immune responses during normal physiological conditions have also been reported, such as during learning (Derecki *et al,* 2010; Filiano *et al*, 2016). Following a learning task, immune cells accumulate in the meninges, exhibiting primarily a type-2 phenotype (Derecki *et al,* 2010, 2011). Unlike in severe inflammatory conditions, however, this response does not result in parenchymal infiltration. Older studies, showing meningeal mast cell degranulation after neuronal stimulation, suggest that neuronal activity can be one of drivers of meningeal immune responses (Dimitriadou *et al*, 1991). On the other hand, there is evidence that meningeal immune responses, such as degranulation of mast cells, can cause neuronal activation in the trigeminal nucleus via meningeal fibers (Chen *et al,* 2014; Karatas *et al,* 2013; Levy *et al,* 2007). Such studies render the meningeal spaces an exciting site for neuroimmune interactions and invite further exploration. We have yet to understand, for example, how meningeal immune responses influence neuronal processes and whether, in the absence of rampant inflammation, they translate into microglial responses. Recent characterization of the meningeal lymphatic vessels provides an exit route for immune cells and CNS antigens, enhancing our understanding of the complexity and regulation of immune responses in the CNS (Aspelund *et al,* 2015; Louveau *et al,* 2015). Recent works describe a previously unappreciated concentration of immune cells along the venous sinuses (Louveau *et al,* 2015), the origin or activity of which is yet unexplored. Given the observed accumulation of amyloid and tau proteins in the CSF long before their

build-up in the parenchyma, are there dysregulated drainage and/or immune responses that may ultimately lead to Alzheimer's disease pathology? Finding answers to such questions may change how we approach the understanding and treatment of neurodegeneration. Although tools for the study of local responses are limited, methods such as the novel application of pharmaceutical modulators of cell trafficking and activation through the thinned skull will facilitate the exploration of immune responses specifically at this site without causing damage to the CNS or widespread peripheral effects (Roth *et al,* 2014).

PERIPHERAL IMMUNITY: RIPPLES OF IMMUNE RESPONSES ON BRAIN HOMEOSTASIS AND FUNCTION

The ability of peripheral immune responses to affect brain function has been increasingly recognized over the past two decades (Dantzer *et al*, 2008; Rook *et al*, 2011; Yirmiya and Goshen, 2011). Perhaps the best documented example is that of sickness behavior, when a peripheral infection or an infection mimic (such as lipopolysaccharide (LPS)) causes a systemic immune response that, together with its accompanying storm of cytokines, affects brain function (Dantzer and Kelley, 2007; Kelley *et al,* 2003). Systemic administration of LPS has been shown to cause broad immune activation in the meninges and choroid plexus, as well as in the brain parenchyma (Chen *et al,* 2012; Gorina *et al*, 2011; Marques *et al,* 2009; Pascual *et al*, 2012; Zhang *et al,* 2014). Microglia and other glia in the brain respond to inflammatory stimuli by further secreting their own cytokines, thus propagating the immune response (Habbas *et al,* 2015; Marques *et al,* 2009; Zhang *et al,* 2014). Parenchymal increase of various inflammatory cytokines has detrimental effects on neuronal activity (such as decreased long-term potentiation) that translates to behavioral deficits in learning, in exploration, or in social interaction (Dantzer and Kelley, 2007; Kelley *et al,* 2003). Another example of immune activity affecting the brain is the maternal immune-activation model for autism, a model based on the strong association of autism diagnosis with maternal infection during gestation (Atladottir *et al,* 2010; Lee *et al,* 2015). In mice, this is contrived by injecting pregnant dams with the viral analog poly(I:C), thereby triggering an inflammatory response that is perpetuated in the pups (Choi *et al,* 2016; Hsiao *et al*, 2012; Smith *et al*, 2007). The mother's transient immune response changes the development and responsiveness of the offspring's immune system, rendering it more inflammatory (Choi *et al,* 2016; Hsiao *et al,* 2012; Smith *et al,* 2007). Overproduction of IL6 and high levels of Th17 cells following the immune response causes abnormal brain development, resulting in impaired neuronal migration and deficits in social interaction (Choi *et al,* 2016; Hsiao *et al,* 2012; Smith *et al,* 2007).

Although studies of inflammation and sickness behavior show that strong immune responses can be detrimental to CNS function, the same can be said of the lack of immune activity (Rook *et al,* 2011; Yirmiya and Goshen, 2011). A large body of literature has documented the finding that mice lacking an adaptive immune system (T and B lymphocytes) show impaired cognitive function and aberrant stress responses (Bartholomaus *et al,* 2009; Brynskikh *et al*, 2008; Derecki *et al,* 2010; Kipnis *et al*, 2004; Marques *et al,* 2009; Marsh *et al,* 2016; Ziv *et al,* 2006; Filiano *et al*, 2016). Such mice demonstrate spatial memory deficits and decreased adult neurogenesis (Derecki *et al,* 2010; Wolf *et al,* 2009; Ziv *et al,* 2006). Reconstitution of immunodeficient mice with a full complement of lymphocytes (through either bone marrow or adoptive transfer) restores their learning ability as well as their neurogenic capacity (Brynskikh *et al,* 2008; Derecki *et al,* 2010; Marsh *et al,* 2016). Interestingly, repopulation with CD4+ T cells alone (but not with CD8+ or B cells) is sufficient to rescue their phenotypes, indicating that helper T cells play an important role in supporting CNS functions (Wolf *et al,* 2009). We have yet to understand precisely how T-cell activity supports brain function, but certain mechanisms may prevent detrimental inflammatory responses in the meninges (Derecki *et al,* 2010, 2011). Intriguingly, recent evidence indicates that in the absence of autoimmune inflammation, T cells specific to CNS antigens may be of preferential importance for brain function (Baruch *et al,* 2013; Radjavi *et al*, 2014; Ziv *et al,* 2006). The role of the adaptive immune system in supporting brain function also becomes apparent during aging. In addition to a decrease in the number of newly generated lymphocytes, an accumulation of FOXP3+ regulatory T (Treg) cells is a hallmark of the aging immune system (Bapat *et al,* 2015; Montecino-Rodriguez *et al*, 2013; Raynor *et al,* 2015; van der Geest *et al,* 2014). Decreased immune activity and accumulation of regulatory T cells are reportedly associated not only with high tumor incidence but also with impaired cognition (Baruch *et al,* 2015; Koronyo *et al,* 2015; Marsh *et al,* 2016; Ron-Harel *et al,* 2008). Evidence suggests that a transient decrease in Treg cell numbers provides a boost in immune activity that benefits behavioral outcomes (Baruch *et al,* 2015; Ron-Harel *et al,* 2008). Although the mechanisms of this phenomenon have yet to be explored, boosting of the immune system may be an attractive option for improving cognitive function.

It should be noted that even though most of the above-cited studies have focused on peripheral immune responses, it is likely that these responses affect immune cells in the meninges and the choroid plexus as well (and possibly even microglia through soluble factors). Although the peripheral component may be sufficient to affect the brain via cytokine mediators acting through circumventricular organs, it is important to distinguish between the immune responses that occur at each site in order to identify the events that initiate them and develop specific treatments. As discussed in the previous section, local activation of mast cells in the meninges is necessary for immune infiltration during stroke (Arac *et al,* 2014). A recent study suggests that after stroke, Th17 cells can migrate from the intestines to the meninges to propagate neuroinflammation (Benakis *et al,* 2016). In this context, understanding the initiating events, timing, and

recruitment sites could enable us to define more precise targets for limiting inflammation after stroke.

CONCLUSIONS

Over the past few decades it has become apparent that not only do the nervous and immune systems interact and influence each other, but also that such crosstalk takes place under homeostatic conditions. Given the parenchymal distribution of resident microglia and the wide repertoire of immune cells in the meninges, in many ways the brain is no different from other organs in terms of its immune presence and surveillance, although meningeal immunity represents an aspect of immune uniqueness of the CNS. Neuroscientists have only quite recently come to appreciate that CNS function is affected by immune activity from embryonic development to aging. We have learned, for example, that brain-resident microglia participate in the pruning and maintenance of neuronal circuits both early in life (during the wiring of the brain) and in adulthood (during processes of learning and refinement). We now also know that the activity of microglia, as well as of other cells of the nervous system, can be affected by signaling from the peripheral immune system. We are just beginning to appreciate the extent to which neuronal activity is influenced by immune system function, and is even dependent on it. Studies to date have shown that, as for peripheral organs, too much (sickness behavior) or too little (aging and immunodeficiency) immune activity is detrimental for CNS function; however, the regulatory mechanisms that balance neuroimmune interactions during homeostatic conditions have yet to be fully identified. We know that the immune system can signal the nervous system via cytokines, and that the nervous system can signal the immune system via innervation of lymphoid organs. We can also envision that 'CNS-conditioned' messages (delivered via cells, vesicles, or molecules) may be able to drain out of the nervous system and further orchestrate supportive immune responses.

The objective of this review was to highlight interactions between the immune and the nervous systems in the course of homeostatic processes such as learning or aging. Although studies addressing these topics are accumulating, the extent of neuroimmune interactions is still far from being understood. Fortunately, we now have more sensitive and a larger array of methods to track both immune and neuronal responses. Thus, we can look forward to the emergence of further studies in which the focus is shifted from models of inflammation to homeostatic processes.

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The authors declare no conflict of interest.

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