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Understanding neuroinflammation through central nervous system infections

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Abstract

Neuroinflammation is now recognized to compound many central nervous system (CNS) pathologies, from stroke to dementia. As immune responses evolved to handle infections, studying CNS infections can offer unique insights into the CNS immune response and address questions such as: What defenses and strategies do CNS parenchymal cells deploy in response to a dangerous pathogen? How do CNS cells interact with each other and infiltrating immune cells to control microbes? What pathways are beneficial for the host or for the pathogen? Here, we review recent studies that use CNS-tropic infections in combination with cutting-edge techniques to delve into the complex relationships between microbes, immune cells, and cells of the CNS.

Introduction

The concept of the central nervous system (CNS) as an ‘immune-privileged’ organ arose in the 1960s with the recognition of the blood-brain barrier. Despite the relative intransigence of this concept, over multiple decades, many studies have challenged it [1]. In addition, the recognition that neuroinflammation potentiates many neurodegenerative diseases [2,3] makes understanding the nuances of neuroinflammation essential. One way to mechanistically define these nuances is by harnessing the processes inflammation evolved to handle: infections. Here, we will review how cutting-edge techniques have offered new insights into the complex interactions between microbes, cells of the CNS, and infiltrating immune cells. We will highlight how these studies challenge dogma about the capabilities of the CNS to generate a functional immune response and the consequences of neuroinflammation.

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Author contribution

Hannah Johnson: Writing – Original Draft, Writing – Review & Editing, Visualization, Funding Acquisition.

Anita A Koshy: Writing – Review & Editing, Visualization, Funding Acquisition, Supervision.

Conflict of interest statement

Nothing declared.

Microglia

Microglia arethe tissue resident macrophages of the brain and thus express many markers that are shared with peripheral macrophages/monocytes. In the noninflamed brain, the segregation of microglia from peripheral myeloid-lineage cells can be done by physical location, morphology, and expression or levels of expression of specific markers (e.g. microglia are $CD11b^{+}CD45^{lo\text{-}intermediate}$ vs. peripheral myeloid cells $CD11b^{+}CD45^{hi}$). Unfortunately, in the setting of inflammation, these distinctions are less absolute and can vary by context. For example, CD11a-expression was recently shown to distinguish infiltrating myeloid-derived cells from microglia in the setting of Alzheimer's disease mouse models and intracranial lipopolysaccharide injection, a component of bacterial cell walls that produces a strong proinflammatory response, but in the setting of chronic infection with *Toxoplasma gondii*, a eukaryotic parasite that naturally infects the CNS of humans and rodents, CD11a was now expressed on microglia [4]. This study highlights how CNS infections drive distinct neuroinflammatory responses and shows the difficulty of separating microglia from infiltrating myeloid cells during fulminant CNS inflammation. Until recently, this gap limited our ability to determine if microglia and infiltrating myeloid cells play overlapping or distinct roles during CNS infection.

Several groups have taken on the challenge of cleanly segregating the roles of microglia and infiltrating myeloid cells in infection. In a *T. gondii* infection model, Batista et al. leveraged the slow turnover of microglia compared to peripheral myeloid-derived cells in combination with a tamoxifen-dependent CX3CR1-Cre driver to generate mice in which only microglia express a green fluorescent protein (GFP). Isolation and profiling of microglia (GFP^{+}) and infiltrating myeloid cells (GFP^{-}) revealed that infiltrating myeloid cells expressed a strong NFκB signature and released inter-leukin (IL)-1β *ex vivo*. Conversely, microglia lacked this NFκB signature and exclusively released IL-1α *ex vivo*. In a series of follow-up studies, this work suggested that IL-1α signaling to the brain vasculature, which expresses the IL-1α receptor, helps to recruit infiltrating immune cells into the *T. gondii*-infected brain (Figure 1a). Collectively, this work is the first to strongly suggest that microglia and infiltrating myeloid cells control *T. gondii* in the CNS through non-overlapping functions [5].

Moseman et al., 2020 also used CX3CR1 tools to reveal a new way in which microglia help control vesicular stomatitis virus (VSV) in neurons. In this study, which used an intranasal inoculation model of VSV, olfactory sensory neurons (OSNs) were shown to be the primary infected CNS cell type and to clear the virus in a non-cytolytic, $CD8^{+}$ T cell-dependent manner. Unexpectedly, the infected OSNs were not the cell type that was activating the virus-specific $CD8^{+}$ T cells. Through a series of experiments in which CX3CR1 was used to mark or deplete microglia, the investigators found that uninfected microglia were acquiring VSV proteins/antigen from infected OSNs and then activating $CD8^{+}$ T cells via microglial major histocompatibility complex (MHC)-I-T cell receptor (TCR) interactions [6] (Figure 1b). While microglial cross presentation has been suggested by a prior study that used whole body irradiation and model antigen injection into the CNS [7], Moseman et al. is the first to rigorously show microglial cross-presentation in a viral infection model.

Another recent approach to define the role of microglia in CNS infection has been systemic administration of PLX5622, a small molecule inhibitor of CSF1R that purportedly selectively depletes microglia, while not affecting peripheral myeloid cells, in non-infectious paradigms [8]. In the setting of viral infection (both peripheral and intracerebral inoculation), PLX5622 administration almost always correlates with higher CNS viral loads and transcriptional changes to infiltrating immune cells, suggesting that microglia potentially help control encephalitic viruses through effects on other immune cells [9–13]. Two recent studies have called these findings into question. One study showed that 14 days of PLX5622 significantly decreased the number of antigen-presenting cells in the blood in uninfected mice [11], while the other showed that prolonged PLX5622 administration caused significant decreases in the absolute numbers of immune cells in the spleen [13]. Thus, until more extensive evaluations of PLX5622's effect on non-microglial immune cells are done, caution should be exercised when interpreting the reliability of PLX5622 to selectively affect only microglia.

Finally, not all microglial responses are beneficial to the host. A prior study of CNS toxoplasmosis found both a decrease in presynaptic clustering of GAD67 and an increase in seizure activity [14]. Follow-up work that included the use of serial block face scanning electron microscopy revealed that *T. gondii*-infected brains showed a loss of perisomatic inhibitory synapses in the hippocampus and layer V of the cortex. There was also an increase in infiltrating myeloid-derived cells and neurons ensheathed by microglia, including perisomatic inhibitory synapses. Using a variety of microglial hallmarks, including GFP-expression in *T. gondii*-infected *Cx3cr1*-GFP mice, these data suggested that in the infected brain, microglia remove perisomatic inhibitory synapses, leading to an increase seizure propensity [15]. The microglial-dependent elimination of synapses is consistent with prior work in West Nile Virus (WNV) encephalitis, in which $CD8^+$ T cell-dependent inter-feron-γ production/release stimulates microglia to prune synapses, resulting in cognitive decline [16,17].

Astrocytes

Astrocytes have long been recognized as important participants in neuroinflammation [18]. A recent study highlighted the role astrocytes play in sensing an invading microbe by studying if the CNS used the alarmin IL-33 as a danger signal in the setting of *T. gondii* infection. Through a series of thoughtful experiments that included bone marrow chimeras and cell-specific deletions of *Il1rl1*—a receptor for IL-33—Still et al. showed that astrocytes both make and respond to IL-33. In turn, this astrocytic IL-33 signaling was important for recruiting T cells and myeloid-lineage cells into the CNS, likely through the downstream production of cytokines and chemokines such as the monocyte attractant *ccl2* [19].

Recent work has also shown that astrocyte inflammatory responses cannot simply be categorized as harmful or helpful. Instead, these responses can vary by inciting stimuli or between astrocytes in different brain regions exposed to the same stimulus [18,20,21]. These regional differences in astrocytic response potentially underlie the clinical observation that the cerebellum is rarely infected with WNV compared to the cortex [22]. As *T. gondii* and several other CNS-tropic microbes also show predispositions for the cortex over the

cerebellum [17,23,24], regional differences in astrocytic responses may have implications for other common neuro-infectious diseases.

This robust astrocytic inflammatory response is thought to prevent astrocytes from harboring latent viruses, but a recent paper suggests that, for certain viruses, astrocytes play a previously unrecognized role in latency. Poelart et al. used neurons that ectopically express the receptor for measles virus (MV) and astrocytes that do not express this receptor to show that neurons are acutely infected, followed by neuron-to-astrocyte transmission of viral ribonucleoproteins through excitatory amino acid transporters (Figure 2). This mode of transmission appears to avoid triggering a type I interferon response and enables MV spread to other astrocytes through membrane fusion, potentially making astrocytes the host cell for chronic MV infection [25]. Why astrocytes are permissive to chronic MV infection is unclear, but this study highlights how microbes exploit the crosstalk between CNS cell types.

Oligodendrocytes

Oligodendrocytes (OLs) have typically not been considered major players in neuroinflammatory responses, though they have long been recognized as the target in immune responses that result in demyelination (e.g., multiple sclerosis and demyelination secondary to mouse hepatitis virus (MHV)). In intracranially inoculated MHV infections, OLs are the most commonly infected cell type but how these infected OLs contributed to the CNS immune response was unknown. Using a recombinant MHV strain that produces Cre recombinase to infect Cre reporter mice that express tdTomato only after Cre-mediated recombination, Pan et al. showed that by 30 days post infection (dpi) — a time point when actively replicating MHV cannot be isolated from the CNS — OLs made up the majority of the tdTomato$^+$ cells in the brain and spinal cord. Interestingly, in the spinal cord, but not the rostral pons, tdTomato$^+$ OLs were associated with demyelinating lesions and infiltrating immune cells, suggesting that demyelination was determined by regional differences in OLs and/or the infiltrating immune cell response to MHV. Transcriptional profiling of brain OLs showed that tdTomato$^+$ OLs had persistent proinflammatory responses at 30 dpi compared to tdTomato$^-$ OLs and that all OLs from infected mice showed an upregulation of myelination genes compared to OLs from uninfected mice. These data suggest that OLs that clear MHV produce a chronic inflammatory state that leads to demyelination which, in turn, drives a compensatory upregulation of myelination genes in all OLs [26].

Neurons

Whether neurons mount traditional immune responses — including the ability to directly stimulate effector/ cytolytic CD8$^+$ T cells — has been the subject of great interest and controversy, in part because neurons show low basal expression of classic immune response genes such as MHC-I or STAT1 [27]. While several microbial studies have shown neuron MHC-I-TCR engagement *in vitro* [28,29], no studies had shown this engagement *in vivo*. To probe neuron MHC-I-TCR engagement *in vivo*, Salvioni et al. generated a B6 transgenic mouse that ubiquitously expresses a floxed copy of an MHC-I allele (H2 L^d) associated with a low CNS *T. gondii* parasite burden. The control of *T. gondii* by this MHC-I allele is driven

by the induction of a robust $CD8^+$ Tcell response to a parasite peptide that is presented in a L^d- restricted manner [30–32]. The authors show that the removal of the L^d allele from neurons only resulted in a higher CNS parasite burden, indirectly suggesting that $CD8^+$ TCR–neuron MHC-I interactions occur *in vivo*. In support of this possibility, transcriptional profiles from laser capture microdissected neurons that had been injected with *T. gondii* protein were enriched for $CD8^+$ T cell transcripts, suggesting that $CD8^+$ T cells lay in extreme proximity to these *T. gondii*-injected neurons [33]. These data are consistent with a recent paper showing that a subset of neurons expressing the influenza glycoprotein hemagglutinin had TCR-neuron MHC-I interactions [34]. How $CD8^+$ T cell activation by neurons leads to the control of *T. gondii* remains unknown, but recent work suggests that cytokine stimulated neurons can clear intracellular parasites using cell-intrinsic, non-cytolytic mechanisms [38].

Recent work has also shed light on the downstream consequences of neuron–T cell interactions and/or cytokine stimulation. Di Liberto et al. used an innovative approach to determine the role of neuron STAT1 — a transcription factor activated by both type I and type II interferons — in $CD8^+$ T cell-dependent neuronal damage. In this approach, neonatal mice are intracranially infected with an attenuated lymphocytic choriomeningitis virus (LCMV) strain that expresses Cre recombinase, leading to a long-term asymptomatic neuronal infection. In late adolescence, the mice are intravenously infected with wild-type LCMV, which induces Tcell-dependent encephalitis that results in neuronal synaptic pruning and motor symptoms. In this unusual paradigm, by infecting $STAT1^{fl/fl}$ mice, the Cre-expressing attenuated LCMV removes STAT1 only in neurons. Through a series of elegant experiments, the authors showed that the activation of neuronal STAT1 signaling leads to an increase in neuronal CCL2, which attracts phagocytic myeloid cells that prune the neuronal synapses [35]. In this paradigm, microglial synaptic stripping did not require C3/C4 complement, contrary to prior work in a WNV encephalitis model [16]. In a Zika virus model, T cell-dependent, interferon-γ mediated activation of microglia led to neuronal apoptosis that eventually resulted in post-infectious cognitive sequelae [17].

Neurons are not without their own internal defense systems. Two recent papers have shown that proteins primarily known for their role in the necroptotic death pathway (ZBP1, RIPK1, RIPK3) can also trigger nonnecroptotic anti-viral responses in neurons [36,37]. One paper demonstrated that WNV-infected or poly IC-stimulated neurons require RIPK1/RIPK3 signaling to generate the maximum production of cytokines such as CXCL10 and CCL2. Notably, this response seems neuron-specific as it was not seen with bone marrow-derived macrophages or microglia. In the setting of subcutaneous or intracranial WNV inoculation, a lack of RIPK3 led to increased mortality and WNV load in the CNS and decreased cytokine production and immune cell infiltration into the CNS [36]. In the second paper, Zika virus infection of neurons stimulated the RIP-activating nucleotide sensor ZBP1, initiating RIPK1/ RIKP3 signaling. With this pathogen, instead of inducing necroptosis, RIPK1/RIPK3 signaling upregulated an immunity related GTPase (IRG1), producing an anti-viral metabolic state via itaconate-induced blockade of succinate dehydrogenase [37]. Neuron-specific antimicrobial pathways appear to be an important line of defense and may become the topic of an increasing number of future studies.

What happens *in vivo* to neurons that clear intracellular pathogens or were manipulated but never infected? Such neurons could not be identified until the advent of Cre-expressing pathogens in combination with Cre reporter mice. Such systems have allowed researchers to identify and begin to profile these neurons. For example, in the study that employed VSV-Cre, virally marked but no longer infected OSNs were present at 50 dpi [6], showing that these neurons cleared the virus by non-cytolytic mechanisms. In a *T. gondii*-Cre model in which neurons injected with parasite protein express GFP regardless of infection status, single cell patch-clamping was used to assess the physiology of GFP^+ neurons compared to nearby, uninjected 'bystander' (GFP^-) neurons in *ex vivo* slices. The bystander neurons had relatively normal electrophysiology while the *T. gondii*-injected neurons were very depolarized and incapable of firing an action potential under normal physiologic conditions, indicating that these neurons were unhealthy and possibly dying. This possibility was confirmed by a 90% reduction in the number of *T. gondii*-injected neurons at 8 weeks post infection compared to 3 weeks post infection [24]. What dictates the survival or death of these neurons remains unclear.

Conclusions

While CNS-tropic microbes often cause high levels of morbidity and mortality, they can also be invaluable tools for teaching us how neuroinflammation works in the brain. These microbes can reveal intricate interactions and non-canonical means for self-defense. By studying CNS-tropic pathogens, which have evolved to handle the CNS immune responses with varying amounts of success, we will continue to learn how our brains handle inflammation.

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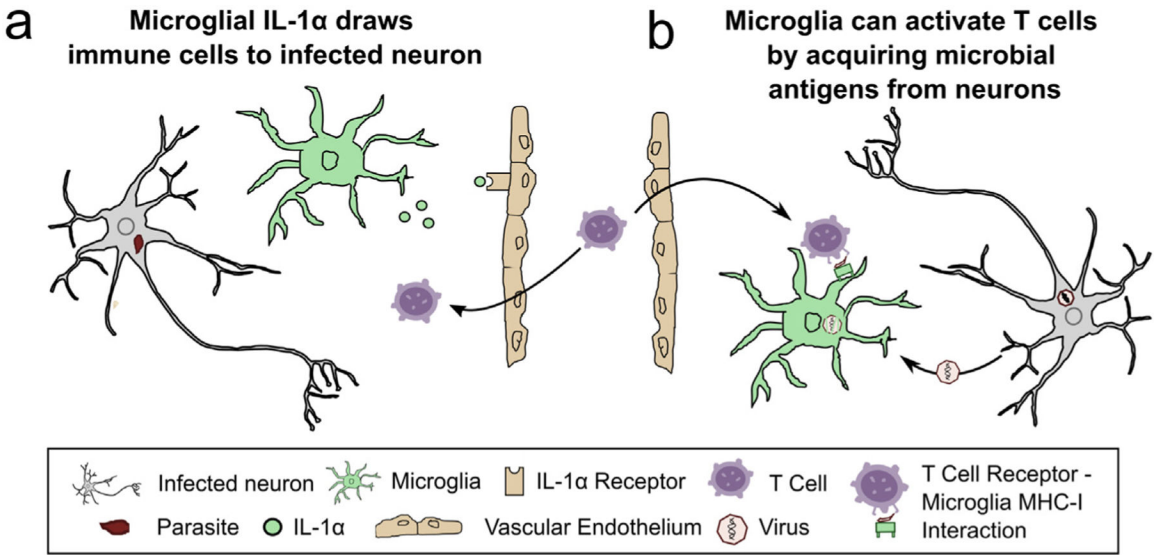

Figure 1. Uninfected microglia recruit infiltrating immune cells and activate pathogen-specific T cells.

(**a**) In *T. gondii*-infected murine brains, microglia release IL-1α onto IL-1α receptors on the vascular endothelium, increasing T cell and myeloid-lineage cell recruitment into the CNS [5]. (**b**) Microglia acquire vesicular stomatitis virus (VSV) antigen from infected olfactory sensory neurons, which is then used to activate effector $CD8^+$ T cells through T cell receptor– MHC-I interactions [6]. MHC, major histocompatibility complex.

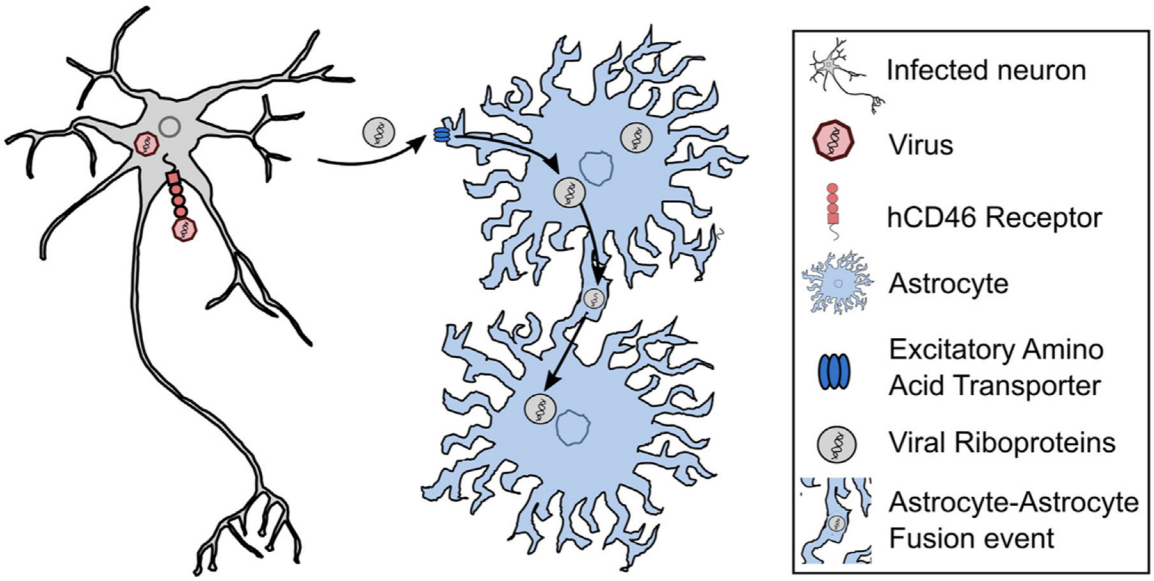

Figure 2. Measles virus neurons transmit measles virus RNA to astrocytes through a non-canonical mechanism.

Measles virus (MV) infects murine neurons that ectopically express the human receptor hCD46. Viral riboproteins (RNP) can then spread to astrocytes that do not express hCD46. This spread requires direct contact with an infected neuron and glutamate/excitatory amino acid transporters. The MV genetic material can then spread from astrocyte-to-astrocyte through astrocyte-astrocyte membrane fusion events [25].