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New advances in immune components mediating viral control in the CNS

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Protective immune responses in the central nervous system (CNS) must act efficiently but need to be tightly controlled to avoid excessive damage to this vital organ. Under homeostatic conditions, the immune surveillance of the CNS is mediated by innate immune cells together with subsets of memory lymphocytes accumulating over lifetime. Accordingly, a wide range of immune responses can be triggered upon pathogen infection that can be associated with devastating clinical outcomes, and which most frequently are due to neurotropic viruses. Here, we discuss recent advances about our understanding of anti-viral immune responses with special emphasis on mechanisms operating in the various anatomical compartments of the CNS.

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Introduction

In contrast to most other organs, the adult mammalian central nervous system (CNS) has a highly limited regenerative capacity and any damage to its structure may result in permanent neurological impairments. It is therefore hardly a coincidence that nature has implemented functional and anatomical barriers to prevent CNS access for pathogens, including viruses. Yet, despite this containment, a wide range of neurotropic viruses are capable to infect the CNS, especially in immunocompromised hosts (Table 1). Thereby, viruses can exploit various entry routes, including transcellular or paracellular transport across CNS barriers or by Trojan horse infection of CNS-infiltrating leukocytes, as recently summarized in more detail [1,2]. Depending on whether viruses spread mainly in the brain coverings or parenchyma, such infections either result in meningitis, encephalitis or both [3]. Animal models of CNS infections have fundamentally shaped our understanding of immune responses governed by the nature of the virus, the type of infected cells and the affected region in the CNS.

For many viruses, a robust innate immune response already at CNS barriers (comprising the meninges, perivascular space and ventricular system) prevents further spread into the subjacent parenchyma (Table 2). At these CNS barriers, specialized macrophage populations, including meningeal, perivascular and choroid plexus macrophages, are collectively referred to as CNS-associated macrophages (CAMs) [4]. Early pathogen detection by CAMs and CNS-resident microglia triggers a disease-associated signature and the release of pro-inflammatory cytokines and chemoattractants [5•6••]. Thereby, CAMs initiate an inflammatory response by recruiting other immune cells, including T cells, neutrophils and monocytes. In line with this, CAMs depletion during CNS infection reduces cell recruitment, while it does not affect local viral load [7]. By contrast, the control and elimination of most viral CNS infections depend on the adaptive immune system which generates distinct memory lymphocyte subsets (Table 2). The latter surveils the CNS to rapidly detect invading or re-activating pathogens and provides immediate responses toward previously encountered antigens.

This review highlights recent findings on immune components mediating viral control during CNS infections taking into consideration the affected anatomical compartment.

Innate immune responses involved in CNS anti-viral responses

Meninges

The meninges refer to distinct membranes enveloping the CNS parenchyma, namely the dura mater, the arachnoid mater and the pia mater that altogether provide a tiered layer of defense. Within the dura mater, a lymphatic system is connected to the cerebrospinal fluid (CSF) via subarachnoid extensions and drains brain interstitial fluid and macromolecules into deep cervical lymph nodes [8••,9]. Tight junctions of arachnoid mater cells physically restrict CNS access for viruses [10].

Table 1

Viruses infecting the central nervous system (CNS) with immune cells implicated in viral control and viral entry routes

Virus family	Human virus	Mouse model virus	Immune cells implicated	CNS access	References
Arenavirus	Lymphocytic choriomeningitis virus (LCMV)	LCMV	T cells	Transcellular	[1]
Coronavirus	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Mouse hepatitis virus (MHV)	Unclear	Retrograde axonal transport	[2]
Enterovirus	Coxsackie virus (CV)	CV	Unclear	Transcellular	[3]
	Poliovirus	Poliovirus	Unclear	Retrograde axonal transport Paracellular	[4,5]
Filovirus	Ebola virus (EBOV)	EBOV	Unclear	Spread from retinal epithelium Leukocyte infection (monocytes)	[6,7]
Flavivirus	Japanese encephalitis virus (JEV)	JEV	T cells	Transcellular Paracellular Leukocytes infection Spread from nasal cavity	[8–10]
	Tick-born encephalitis virus (TBEV)	TBEV	T cells, B cells, innate	Transcellular Paracellular	[11–13]
	West Nile Virus (WNV)	WNV	CD8+ T cells	Transcellular Paracellular Leukocyte infection (neutrophils) Retrograde axonal transport	[14–16]
	Zika virus (ZIKV)	ZIKV	T cells	Paracellular	[17,18]
Herpesvirus	Cytomegalovirus (CMV)	Mouse cytomegalovirus (MCMV)	T cells	Spread from meninges in IC hosts	[19,20]
	Epstein Barr Virus (EBV)	EBV	Unclear	Leukocyte infection (B cells)	[21]
	Herpes simplex virus (HSV-1/HSV-2)	HSV	T cell	Paracellular Retrograde axonal transport	[5,22]
Orthomyxovirus	Influenza A virus (IAV)	IAV	Unclear	Paracellular Retrograde axonal transport	[23,24]
Paramyxovirus	Measles virus	Measles virus	T cells	Transcellular	[5]
Parvovirus	Adeno-associated virus (AAV)	AAV	Unclear	Leukocyte infection (T cells)	[25]
Picornavirus	Theiler's encephalomyelitis virus (TEV)	Theiler's murine encephalomyelitis virus (TMEV)	Unclear	Retrograde axonal transport	[26]
Polyomavirus	John Cunningham Virus (JCV)	Murine Polyomavirus (MuPyV)	T cells	Leukocyte infection	[27]
Retrovirus	Human immunodeficiency virus (HIV)	HIV	Unclear	Paracellular Leukocytes infection (CD4 cells)	[28,29]
	Simian immunodeficiency virus (SIV)	SIV	Unclear	Leukocyte infection (PVM)	[30]
Rhabdovirus	Rabies virus	Rabies virus	Unclear	Paracellular Retrograde axonal transport	[31,32]
	Vesicular stomatitis virus (VSV)	VSV	Unclear	Retrograde axonal transport	[33]
Togavirus	Chikungunya virus	Chikungunya virus	Unclear	Transcellular	[34]
	Sindbis virus (SINV)	SINV	Unclear	Retrograde axonal transport	[34]

PVM: perivascular macrophages.
IC: immune-compromised.
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Table 2

CNS location of innate and adaptive immune cell types

CNS compartment	Innate immune cell types	Adaptive immune cell types
Meninges	Dural M, pial M, cDC1, cDC2, pDC, migDC?, mast cells?	circT cells, ASC
Choroid plexus	CPM, epi-CPM, cDC1, cDC2, migDC?,	circT cells
Perivascular space	PVM	ASC
Parenchyma	Microglia, blood-derived macrophages	TRM, TEM?, ASC

M: macrophages.
cDC: conventional dendritic cells.
pDC: plasmacytoid dendritic cells.
migDC: migratory dendritic cells.
CPM: choroid plexus macrophages.
Epi-CPM: macrophages located in the apical surface of the choroid plexus epithelium.
PVM: perivascular macrophages.
circT: circulating T cells.
ASC: antibody-secreting cells.
TRM: tissue-resident memory T cells.
TEM: effector memory T cells.

The meninges harbor dense populations of CD206+ dural and pial macrophages [11] (meningeal macrophages, MMs) that survey their environment and support robust inflammatory responses. MMs are tissue-resident cells that are not replenished by blood monocytes in the healthy CNS [12]. Those long-lived MMs can be infected by viral pathogens such as lymphocytic choriomeningitis virus (LCMV) [13••] and are also potential reservoirs for persistent infections such as human immunodeficiency viruses (HIV) [14]. Furthermore, following infection with attenuated LCMV in mice, MMs are depleted and replaced by inflammatory monocytes that locally differentiate into CD206+ macrophages [13••]. Of note, following engraftment, macrophages retained an altered signature that affected their microbial sensing, highlighting the dynamism of the meningeal niche in the context of infections and supporting the concept of innate memory in this compartment. Multiple subsets of dendritic cells (DCs) are identified in murine meninges, including conventional DCs (cDC1 and cDC2) and plasmacytoid DCs (pDCs) [6••]. Interestingly, a subset with a gene signature resembling migratory DCs was detected in the dural meninges as well. Upon infection, these DCs may access dural lymphatics and reach draining lymph nodes to initiate adaptive immune responses. These recent findings reshaped our understanding how meningeal immune responses are connected to the peripheral immune system and about the immune privilege attribute of the CNS.

Perivascular space

Cerebral vessels possess ramifications penetrating the CNS that form the neurovascular unit (NVU) [2]. This highly specialized microvasculature is an integral component of what is commonly referred to as the blood brain barrier (BBB), a potent physical barrier that restricts CNS access. Infections with neurotropic viruses are often associated with a disruption of the BBB, either by infection of cell types forming the NVU or by the release of cytokines and/or chemokines from infiltrating activated leukocytes [15]. For instance, in the rabies-virus-infected mouse brain, the pro-inflammatory cytokine interferon-gamma (IFN-γ) has the potential to interfere with the BBB permeability *in vivo* and to disrupt tight junctions *in vitro* [16].

Perivascular macrophages (PVMs), similarly to MMs, are long-lived CD206+ tissue-resident cells that act as first line defense against invading pathogens and regulate cell infiltration within the CNS [17]. During neuroinflammation in mice, PVMs were recently shown to acquire a disease-associated signature, characterized by upregulation of CD74 and CCl5 [5•], likely contributing to leukocyte recruitment. Although the main role of PVMs is to prevent viruses from accessing the CNS, they can also serve as a reservoir for latent viral infections such as HIV and can become the immunological target of CD8+ T cells [18]. Additionally, during simian immunodeficiency virus (SIV) infection in macaques, the proliferation of infected CNS PVMs results in macrophages' accumulation in the perivascular space and development of encephalitic lesions [19].

Ventricular system

The CSF is secreted by the choroid plexus (CP) situated in ventricles of the brain. The fenestrated CP capillaries represent an important entry site for pathogens into the CP stroma while epithelial cells lining the CP stroma are interconnected by tight junctions and represent the blood-CSF-barrier (B-CSF-B) [20]. Since pathogens can access the CP stroma, their detection at this site must be rapid in order to avoid as much as possible viral spread in the CSF and in the subventricular zone (SVZ). Stromal CP macrophages (CPMs) have a common origin with other CAMs, while macrophages located in the apical surface of the CP epithelium (epi-CPMs) were recently proposed to be ontogenically related to microglia [6••]. In the same study, epi-CPMs have a very high phagocytic activity *in vitro*, suggesting an efficient sampling of their environment. In the healthy mouse brain, subsets of cDC1 and cDC2 are also described in the CP [6••,21]. Recently, single-cell RNA-sequencing (scRNA-seq) analysis of the mouse brain identified DCs with a gene signature evocative of migratory DCs in the CP [6••], although their functional ability to migrate and reach draining lymph nodes has not been evaluated. Altogether, the recent identification of such CP-associated phagocytes revealed the complexity underlying CNS border immunity, which needs to be elaborated in future studies.

Ependymal cells that line the ventricles of the brain represent an additional physical barrier to restrict the spread of viruses within the SVZ. The SVZ, located just below the layer of ependymal cells, contains neural stem cells and progenitor cells that ensure neurogenesis in the adult brain [22–24]. In humans, the CSF is in close vicinity to those neural stem cells and can directly impact their proliferation [25]. Thus, damages to this neurogenic niche and in particular the destruction of ependymal cells during viral infections might expose SVZ cells to CSF and have disastrous consequences for brain homeostasis and repair.

Furthermore, the murine CP is the preferential location of group 1 innate lymphoid cells (ILC1) during steady-state, although also detectable in the meninges and to a lower extend in the brain parenchyma [26]. Their early release of IFN-γ upon neuroinflammation likely stimulates mononuclear phagocytes and initiates a tissue-wide anti-viral state in the infected tissue. Since ILC1 and natural killer (NK) cells express similar levels of NKp46 and NK1.1 [27], they were often confounded and evaluated as a common population. Nowadays, ILC1 and NK cells are discriminated by expression of surface markers CD49a and CD49b, respectively [26]. However, effector mechanisms of ILC1 during CNS viral infection has not been specifically addressed. During autoimmune CNS inflammatory disease in mice, ILC1 are recruited from the CP and the meninges to the brain parenchyma, a phenomenon associated with local upregulation of CXCL9, CXCL10 and CXCL16 in the inflamed brain [26]. Thus, one may speculate that ILC1 serve as migratory cells rapidly producing IFN-γ at infection site.

Olfactory bulb neuroepithelium

The nasal cavity is in close proximity to the olfactory bulb (OB) and represents an entry portal to reach the CNS through retrograde axonal transport via olfactory sensory neurons (OSNs). Respiratory viruses, including influenza A virus, reach the CNS mainly in immunocompromised hosts [28], suggesting that appropriate immune responses are key in preventing virus entry at this border site. A recent study of intra-nasal vesicular stomatitis virus (VSV) infection in mice revealed an important role of microglia in orchestrating neuroprotection from the nasal cavity [29••]. In this setting, microglia acquired viral antigens from infected neurons and presented them to infiltrating virus-specific CD8+ T cells, eliciting potent virus elimination.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is causing the worldwide pandemic, has been detected in the brain of some of the COVID 19 patients [30]. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a cellular receptor for host cell entry [31]. This receptor is expressed at varying levels in the olfactory epithelium [32], suggesting a possible CNS portal of entry. CNS access of SARS-CoV-2 via the nasal cavity is furthermore supported by the recent identification of SARS-CoV-2 RNA and S protein in the in OSNs of the olfactory epithelium of COVID-19 patients that succumbed to infection [33]. Additionally, the expression of ACE2 seems to be expressed in the human brain microvasculature [34], which could explain why a fraction of COVID-19 patients suffer from cerebrovascular complications [35]. Beyond ACE2, neuropilin-1 (NRP-1) is an additional host factor involved in SARS-CoV-2 cell entry, since blocking its interaction with SARS-CoV-2 results in reduced viral infection *in vitro* [36]. Its *in vivo* role as receptor for SARS-CoV-2 remains however to be elucidated.

The emergence of novel viruses targeting the brain via the OB neuroepithelium highlights the necessity to better understand immune reactions occurring at this interface.

CNS parenchyma

NK cells represent 1% of total leukocytes in the healthy mouse brain [37] and are one of the first effector cells at sites of inflammation. In human, NK cells deficiencies are associated with high susceptibility to herpes virus encephalitis [38,39] and are described for several CNS infections [40–45]. NK cells produce IFN-γ in the brain during viral encephalitis [46], stimulating macrophages and microglia and thereby shaping anti-viral responses. In addition, NK cell activation is sufficient to protect mice from fatal neurotropic Sindbis virus infection [47], highlighting NK cells crucial role in such infections.

Microglia are a well-studied parenchymal resident population of innate immune cells ontogenetically distinct from other tissue macrophages [48] and are among the first responders to pathogen invasion [49]. In herpes simplex virus (HSV)-infected mice, microglia are essential for protective antiviral immunity as their depletion is accompanied by higher viral load and an increase of disease severity [50]. During CNS viral infection and the resulting inflammation, the pool of microglia is often enriched by engrafted blood-born monocytes which participate to the host defense in the CNS [51]. Thereby, microglia adopt an activated phenotype partially via interferon alpha/beta receptor (IFNAR) signaling characterized by proliferation, acquisition of an amoeboid morphology and the downregulation of homeostatic markers [52,53]. However, microglia also contribute to immunopathology during viral encephalitis. Of note, complement proteins mediate synaptic pruning by microglia during early stages of CNS development [54,55]. During peripheral arbovirus and flavivirus infections in mice, complement activation is essential to minimize viral spread to the CNS [56,57]. Unfortunately, although complement proteins are increased in the CNS in mouse models of encephalitis [58,59], their local implications in viral

control remain elusive. By contrast, microglia participate to complement-dependent synapse elimination post West Nile virus (WNV) encephalitis in mice [59]. During recovery from WNV and ZIKV infections in mice, T-cell-derived IFN-γ signaling in microglia results in hippocampal synaptic stripping that is associated with cognitive sequelae [60•]. Synaptic loss mediated by microglia and blood-derived macrophage is also observed following neuronal infection by LCMV in mice, where it occurs via neuronal IFN-γ receptor (IFNGR) signaling and downstream STAT1 activation [61,62•]. One may speculate that such a defense mechanism serves to limit retrograde trans-synaptic viral spread at the expense of disconnecting neurons from their functional network. However, neurotropic viruses have developed strategies to overcome interferon signaling by inhibiting or degrading key molecules (e.g. TYK2, STAT2, IFIT, etc.) involved in the downstream signaling cascade [63,64]. In an autopsy of human fetal brain infected with ZIKV, microglia released high levels of pro-inflammatory mediators including IL-6, TNF, IL-1β, and CCL2 and participated to the loss of neuronal progenitors, thus contributing to microcephaly [65]. Thus, it appears clear that while beneficial in creating an anti-viral state during viral infection, IFN-γ signaling can also have detrimental effect in the CNS by interfering with existing synaptic network.

Adaptive immune cells involved in CNS anti-viral responses

T cells

Following CNS infections, both CD4+ T helper type 1 (T_H1) cells and CD8+ T cells infiltrate the infected area and contribute to the anti-viral response. It was recently described in an *in vitro* study that human T_H1 cells from patients with a neuroinflammatory disease have a better ability to cross the BBB than the B-CSF-B [66]. T_H1 cells mainly produce inflammatory cytokines to activate other immune cells, while CD8+ T cells exert in addition cytotoxic functions to directly eliminate infected cells. However, recent studies suggest that this classical view may not reflect the full spectrum of CD4+ T cell functions and propose instead that these cells could also exert cytotoxic function in the CNS [67•,68,69], but the formal demonstration thereof is still awaiting further investigations.

T cells use different mechanisms to fight viral infections in the CNS. Among them, T cells release IFN-γ, a critical cytokine for innate and adaptive responses. Functions of IFN-γ include the induction of a tissue-wide anti-viral state [70,71] and the local activation of immune cells, such as microglia and macrophages [72]. Following mouse hepatitis virus (MHV) infection in mice, T cells in the brain not only promote inflammatory reactions but also impede them by the production of anti-inflammatory cytokine such as IL-10 to avoid excessive tissue injury [73]. In this regard, antibody-mediated blockade of the IL-10R signaling in mice exacerbates brain tissue damage and enhances immune cell infiltration in the brain following Theiler's murine encephalomyelitis virus (TMEV) infection [74].

The cytotoxic capability of CD8+ T cells mainly relies on the release of perforin-containing and granzyme-containing granules, inducing apoptosis-mediated cell death via several distinct mechanisms [75–77]. Degranulation-mediated cytotoxicity involves the recognition of the cognate antigen on MHC-I-expressing cells [78] and a single CD8+ T cells can kill numerous infected cells [79]. Depending on the virus and cell-type infected in the CNS, the prevailing immune mechanism responsible for viral clearance can vary. For instance, while CD8+ T cells eliminate LCMV and MHV from microglia and astrocytes through cytotoxic mechanisms, non-cytolytic viral clearance has been observed in infected ependymal cells and oligodendrocytes after LCMV and MHV, respectively [80,81]. Furthermore, granzyme-B-expressing CD8+ T cells were found to cluster around infected neurons without inducing cell death during reactivation of HSV-1 [82,83], whereas, in other virus infection contexts destruction of infected neurons were more extensive [84,85]. Of note, neurons can adopt an antiviral metabolic state to restrict ZIKV replication in mice [86••], reflecting CNS inherent strategies to resist virus infection. A role for T cell-derived IFN-γ has been proposed to mediate non-cytolytic viral clearance [70]. Altogether, these observations suggest that immune responses are tailored to minimize irreversible cell loss in the fight against CNS infection. Yet, factors favorizing either cytotoxic or non-cytolytic virus clearance in the CNS remain incompletely understood. In this regard, neuronal and glial cells participate in the maintenance of tissue integrity by expressing programmed death-ligand 1 (PD-L1) [70] and/or Fas-L [87–89], which interfere with T cell activation and T cell survival, respectively. Hence, T cells and CNS resident cells both contribute to fine-tuning anti-viral immune responses that either resolve acute infections or control persistent infections, with the subsequent generation of T cell memory subsets.

Subsets of circulating and non-circulating memory T cells surveil distinct anatomical niches in the CNS during steady state (Table 2). In contrast, naive T cells hardly patrol the CNS under homeostatic condition. Circulating memory T cells predominantly patrol the CP and the meninges [90–93], while non-circulating tissue-resident memory T (T_{RM}) cells inspect the brain parenchyma [94]. As in mice, T cells populating the human brain with a T_{RM} phenotype have been identified [95••]. Although brain T_{RM} (bT_{RM}) were originally thought to reflect traces of past neurotropic viral infections, they are also described during persistent CNS infection in mice [96] and it was recently shown that peripheral infections can

also generate bT_{RM} [97••]. Of note, in mice, during persistent polyomavirus infection of the CNS, bT_{RM} differentiation requires local virus-specific CD4-derived IL-21 [98], while this prerequisite for CD4-help is not needed following acute LCMV infection [99]. Interestingly, bT_{RM} cells are not disseminated through the brain parenchyma but are preferentially localized in vicinity to surface-associated structures, such as perivascular and periventricular regions [99]. This localization at pathogen entry sites seems preferred by bT_{RM} to immediately detect viral reinfection [94,99] or reactivation [96,100]. Of note, bT_{RM} are sufficient to protect mice from lethal LCMV re-infection, using a combination of perforin and IFN-γ mechanisms [99]. Similarly, bT_{RM} can control murine cytomegalovirus (MCMV) reactivation in neonatally infected mice [100]. Since bT_{RM} express high-affinity T cell receptors (TCRs) [96], they might be able to be reactivated by low levels of viral antigens. In contrast to T_{RM} from other organs, bT_{RM} express high levels of the inhibitory receptor programmed cell death protein 1 (PD-1) [101]. Lung T_{RM} are rapidly reactivated by non-professional antigen-presenting cells during infection [102]. Thus, maintenance of PD-1 expression on bT_{RM} could constitute a safety mechanism by which reactivation of these highly cytotoxic and potential harmful cells may be prevented in the CNS. Additionally, CD8 + T cells with a T_{RM} phenotype were shown to mediate persistent neurological deficit following WNV and ZIKV infections by continuously producing IFN-γ and thereby promoting microglia-mediated synaptic stripping [60•]. Thus, while playing an important protective role against recurrent CNS infections, bT_{RM} appear to represent a double-edged sword which might be involved in chronic neuroinflammatory diseases, including CNS autoimmunity [103•]. However, bT_{RM} can also be found in the CNS of healthy donors [95••], and thus their implications for such chronic neuroinflammatory conditions require further investigations.

B cells (Abs)

Viral infections of the CNS trigger virus-specific antibodies as can be detected in the blood serum but also in the CSF of infected hosts. With regard to the latter, B cell accumulation has been described in the CNS during the acute phase and chronic stages of CNS infections in which these cells are retained as antibody-secreting cells (ASCs) and memory B cells (Bmem) [104–106] (Table 2). Those ASCs exert local protective role after numerous neurotropic infections, including Sindbis virus, Semliki forest virus, WNV, rabies virus, coronavirus and MCMV infections [104,107,108], although precise mechanisms conferring protection remain unclear. Of note, those studies were performed on entire brain tissue and the exact localization of ASCs was not assessed. Recently, ASCs subsets were described in the meninges, the perivascular space and in the brain parenchyma [109] and they seemed to be maintained by homeostatic proliferation, independently of follicle formation [109]. Since
T-cell dependent priming of virus-specific B cells is crucial for their differentiation [110], B cell priming likely occurs in secondary lymphoid organs and only after ASCs subsets enter the CNS. Since pDCs are well known to be involved in the generation of plasma cells [111], one may speculate that pDCs localized in the meninges could also be involved in local plasma cells differentiation, although this requires further investigation.

Production of neutralizing antibodies has been suggested to be involved in controlling persistent CNS viral infections at latent [110,112] and chronic stages [113] but little is known concerning their precise contribution. For instance, in MCMV chronic infection, B cell numbers increase throughout the latent phase of infection and control the spread of reactivated virus [114]. In MHV-A59 strain infection, a persistent gliatropic virus causing a chronic demyelinating disease, persistence of IgM-producing B cells in the brain is crucial for long-term viral protection [110]. Thus, the role of antibodies in the CNS following infections is probably to reduce viral spread rather than to contribute to local elimination of infected cells.

A more precise understanding of B cell behavior during CNS infections is therefore necessary to better understand how these cells could be involved in anti-viral immune responses of the CNS.

Conclusion

The last years have provided interesting new insights into regulation and processes of immune responses during viral CNS infections. It became apparent that the virus type and infected cells in the CNS strongly influence the resulting immune reactions with regard to their quality and quantity. However, our understanding about the individual cellular and molecular players contributing to protective immunity remains still incomplete. Thus, recent descriptions of ontogenically different innate immune cells but also resident T cells in different compartments of the CNS open up new possibilities to better dissect how the immune system copes with different viral CNS infections. In addition, high antiviral antibody titers and the recent description of ASCs persisting in the CNS during viral infections indicate local functions of B-cell subsets and antibodies for antiviral immune responses in the CNS. In this regard, we believe it is important to further investigate how such cellular and humoral immune responses may be involved in neurological short-term and long-term sequelae often observed after viral CNS infections, and how such potentially compartmentalized inflammatory responses, some of which are clinically silent, might represent a fertile ground for other neurological chronic diseases such as multiple sclerosis or schizophrenia [103•,115,116].

Altogether, a better understanding of how anti-viral immune responses are tailored to rapidly detect viral invasion and strive for viral control while minimizing collateral tissue damage of the CNS may guide future protective and therapeutic interventions.

Conflict of interest statement

Nothing declared.

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