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Immune Responses to Viruses in the CNS

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Glossary

Astrocyte Glial cell that secretes neuroprotective factors and is associated with maintenance of the BBB.
Blood–Brain Barrier Endothelial cells connected by tight junctions that form a highly selective barrier between the circulating blood and the CNS parenchyma.
Central Nervous System In vertebrates, it comprises the brain and spinal cord; the complex of nerve tissues that controls the activities of the body.

Abstract

For recovery from infection, the immune response in the central nervous system (CNS) must eliminate or control virus replication without destroying nonrenewable, essential cells. Thus, upon intracellular virus detection, the infected cell must initiate clearance pathways without triggering neuronal cell death. As a result, the inflammatory response must be tightly regulated and unique mechanisms contribute to the immune response in the CNS. Early restriction of virus replication is accomplished by the innate immune response upon activation of pattern recognition receptors in resident cells. Infiltrating immune cells enter from the periphery to clear virus. Antibodies and interferon-γ are primary contributors to noncytolytic clearance of virus in the CNS. Lymphocytes are retained in the CNS after the acute phase of infection presumably to block reactivation of virus replication.

Immune Response in Central Nervous System

For recovery after virus infection of the central nervous system (CNS), the essential, nonrenewable nature of neurons requires a fine-tuned immune response that controls virus replication without damaging neuronal function. Damage can result directly from virus replication or from the host immune response to infection. Functional impairment or loss of neurons following infection can be fatal or leave survivors with neurological sequelae including cognitive deficits, seizures, or paralysis (Hart et al., 2014; Griffiths et al., 2013; Silverman et al., 2013; Ooi et al., 2008; Sauder et al., 2001; Finley et al., 1955). Thus, the immune responses required for successful clearance and control of virus infections in the CNS are often distinct from those required for clearance from other organs and are characterized by noncytolytic, virus-specific processes. This strategy preserves CNS function and minimizes the likelihood of autoimmunity. Many viruses can infect the CNS, including DNA viruses, plus- and minus-strand RNA viruses, and retroviruses, leading to varying outcomes from disease. DNA viruses, such as herpesviruses (reviewed in Koyuncu et al., 2013), often establish a latent infection as opposed to RNA viruses that generally lack a nuclear phase for their replication cycle and cause acute disease. In this article, we will focus on RNA virus infections in the CNS (Table 1).

Mouse Models of Infection

Much of our knowledge about the immune response to neurotropic viruses comes from studying well-characterized mouse models of infection. Studies have investigated the course of disease and immune response both in immunocompetent mice and animals deficient in specific components of the immune response. These studies have provided detailed knowledge of the role of each arm of the immune response in control of virus replication and spread, virus clearance, and in immunopathology. In all infections, outcome of infection is dependent on the age and genetic background of the mouse and the strain of the virus used. For simplicity, we will focus on the most commonly studied strains of each virus family and infection of mature mice. Detailed studies of immune responses to neurotropic viruses have included neuronal infections with rabies virus, flaviviruses, and alphaviruses, as well as infection of multiple cell types with natural mouse pathogens such as Theiler’s murine encephalomyelitis virus (TMEV), mouse hepatitis virus (MHV), and lymphocytic choriomeningitis virus (LCMV).

The immunological processes required for virus clearance from the CNS are cell type and virus specific. Experimental approaches to define these clearance mechanisms are dependent on the transient depletion of specific immune cell populations and on the use of mice that have selective deficiencies in various components of the immune system. Because of the interdependent relationships of components of the immune system in the development of an immune response, deficiencies of one type of cell or molecule may affect several facets of the immune response, making it difficult to identify specific effectors that are crucial for in vivo clearance.
Entry into the CNS

Infection is rarely initiated in the CNS because viruses must invade the CNS from initial sites of infection in the periphery with induction of the immune response in peripheral lymphoid tissues. Entry of viruses, immunoglobulins, and immune cells from the blood is restricted by the blood–brain barrier (BBB), a selectively permeable barrier with tight junctions between cerebrovascular endothelial cells that are supported by astrocytes (Figure 1). The BBB separates the parenchyma of the CNS from the circulating blood and serves as a physical blockade to bloodborne infections of the CNS. However, the endothelial barrier is more permeable at certain sites in the CNS (e.g., choroid plexus) and in inflammation increases permeability to allow immune cell infiltration along with opportunities for virus entry. Historically, routes of CNS infection have been deduced from data obtained by histological staining at early times after infection or disruption of a potential route of infection. Entry routes are not mutually exclusive, as multiple routes have been described for some viruses. Recently, new techniques such as intravital microscopy and CLARITY preparation of infected brains have been developed that may lead to new insights on the mechanisms of CNS entry (Yang et al., 2014; Chung et al., 2013; McGavern and Kang, 2011).

In general, virus entry is either from the periphery by neuronal axonal transport or from the bloodstream across the vascular endothelium. Sensory and motor neurons extend their processes into the periphery and provide a point of entry for some neurotropic viruses replicating in peripheral tissue. Expression of viral receptors on neuromuscular junctions facilitates entry of poliovirus, adenovirus, and rabies virus into the CNS (Salinas et al., 2010). Olfactory neurons that project into the respiratory mucosal epithelium can provide a direct route to the brain for alphaviruses (Phillips et al., 2013; Powers and Logue, 2007; Charles et al., 1995), flaviviruses (Yamada et al., 2009; Monath et al., 1983), coronaviruses (Barnett and Perlman, 1993), paramyxoviruses (Munster et al., 2012), bunyaviruses (Bennett et al., 2008), and occasionally influenza virus (van Riel et al., 2014). Hematogenous entry occurs when a virus directly infects BBB endothelial cells or infects leukocytes that cross the BBB providing entry by a ‘Trojan horse’ mechanism (Neal, 2014; Wilson, 2013; Rhoades et al., 2011; Kim, 2003; Haase, 1986).

### Immune System in the Uninfected CNS

The CNS is relatively protected from immunologic activity. In addition to the physical protection by the BBB, the brain parenchyma has no lymphatic vessels or professional antigen-presenting cells, low expression of major histocompatibility complex (MHC) molecules, and active maintenance of an immunologically quiescent state. However, the exclusion of immune cells and the role of active immune signaling in the CNS has been redefined recently (Schwartz et al., 2013; Muldoon et al., 2013; Elmer and McAllister, 2012; Hernangómez et al., 2012). Resident cells in the nervous system, including neurons, play an active role in the immune response (Schultz et al., 2013; Muldoon et al., 2013; Elmer and McAllister, 2012; Hernangómez et al., 2012). Resident cells in the nervous system, including neurons, play an active role in the immune response (Schultz et al., 2013; Muldoon et al., 2013; Elmer and McAllister, 2012; Hernangómez et al., 2012).

### Immunity to Viral Infections

#### Immune Responses to Viruses in the CNS

| Family | Virus | Primary target cell in CNS |
|--------|-------|----------------------------|
| (+)ssRNA | Coronaviridae | Mouse hepatitis virus* |
| | | Neurons, microglia, astrocytes, oligodendrocytes |
| | Flaviviridae | Japanese encephalitis virus |
| | | Neurons |
| | | West Nile virus* |
| | | Neurons |
| | | St. Louis encephalitis virus |
| | | Neurons |
| | Picornaviridae | Coxsackie virus |
| | | Meninges |
| | | Poliovirus |
| | | Motor neurons |
| | | Enterovirus 71 |
| | | Neurons |
| | | Thielier’s murine encephalitis virus* |
| | | Neurons, microglia, oligodendrocytes |
| | Togaviridae | Eastern equine encephalitis virus |
| | | Neurons |
| | | Venezuelan equine encephalitis virus |
| | | Neurons |
| | | Sindbis virus* |
| | | Neurons |
| (-)ssRNA | Arenaviridae | Lymphocytic choriomeningitis virus* |
| | | Neurons, astrocytes, oligodendrocytes, ependyma |
| | Bornaviridae | Bornavirus |
| | | Choroid plexus, meninges, neurons |
| | | Neurons, astrocytes, oligodendrocytes, ependyma |
| | Bunyaviridae | LaCrosse virus |
| | | Neurons |
| | Paramyxoviridae | Nipah virus |
| | | Ependyma |
| | | Measles |
| | | Neurons, ependyma |
| | | Mumps |
| | | Meninges, ependyma |
| | Rhabdoviridae | Rabies |
| | | Neurons |
| | | Neurons |
| | Retroviridae | Vesicular stomatitis virus* |
| | | Neurons |
| | | HIV |
| | | Microglia |
| | | Human T lymphotrophic virus I |
| | | Astrocytes |

*Commonly used in mouse models of viral encephalitis.
Jackson et al., 2006). Additionally, memory T cell and B cell are found in the CNS long after infectious virus has been eliminated (Phares et al., 2013; Metcalf et al., 2013; Wakim et al., 2010; Wilson et al., 2010).

Resident cells monitor the CNS for infection and initiate and control inflammation when infection occurs. Microglial cells, the resident macrophages of the CNS, express the CD200 receptor (CD200R), TREM2, CD172a, and CD45 and are kept in a quiescent state through interactions with electrically active, healthy neurons expressing CD200, HSP60, CD47, and CD22 and through the production of neurotrophins (Chavarría and Cárdenas, 2013; Ransohoff and Cardona, 2010; Hoek et al., 2000). Local production of the anti-inflammatory cytokines transforming growth factor (TGF)-β and IL-10 by astrocytes, pericytes, and meningeal cells further inhibits cellular activation (Schwartz et al., 2013; Fabry et al., 1995; Johnson et al., 1992). Activated T cells cross the BBB into the CNS for immunological surveillance upon interactions with P-selectin on endothelial cells, but leave or die if antigen is not encountered (Irani and Griffin, 1996; Wekerle et al., 1991, 1986).

The Innate Immune Response

The innate immune response initiated by resident cells in the CNS upon virus infection is the first line of defense (Figure 2(a)). Detection of infection occurs through activation of cellular pattern recognition receptors that include the Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs). Microglia, as the professional immune cells of the CNS, express all of the known pattern recognition receptors. Additionally, neurons, astrocytes, and to a lesser extent oligodendrocytes, express selected pattern recognition receptors and thus contribute to innate immune signaling (Kigerl et al., 2014).

Engagement of TLRs and RLRs activates the transcription factors IRF-3, IRF-7, and NFκB that control expression of type-I interferon (IFN)-α and IFN-β. For many CNS infections, IFN production is critical for early control of infection. Mice deficient in type-I IFN signaling, IFNAR1−/−, have increased virus replication and mortality upon infection by a variety of viruses including Sindbis virus (SINV), West Nile virus (WNV), LCMV, and vesicular stomatitis virus (Samuel and Diamond, 2005; Byrnes et al., 2000; Ryman et al., 2000; Müller et al., 1994). Moreover, pretreatment with IFN is protective (Frolov et al., 2012; Lucas et al., 2003; Grieder and Vogel, 1999; Després et al., 1995a). IFN signaling must be tightly regulated as excess IFN, particularly IFN-α, can be neurotoxic (Nallar and Kalvakolanu, 2014; Reyes-Vázquez et al., 2012). In contrast, IFN-β coordinates the immune response and is generally neuroprotective (McLaurin et al., 1995).

Autocrine and paracrine binding to the ubiquitously expressed IFNα/β receptor initiates JAK/STAT signaling and directs IFN-stimulated gene (ISG) expression. ISGs restrict virus replication in infected cells and establish an antiviral state in neighboring cells to limit virus spread. Although IFN signaling stimulates the expression of hundreds of ISGs, antiviral effects...
of these proteins are both virus specific and tissue specific (Cho et al., 2013a; Diamond and Gale, 2012; Schoggins et al., 2011; Zhao et al., 2011). For instance, the ISG Ifi2 restricts WNV in some regions of the brain, but did not affect replication in the cerebral cortex, spinal cord, or periphery (Cho et al., 2013b).

Engagement of NLRs by infecting viruses can initiate inflammasome formation in the CNS. The inflammasome activates caspase-1 to cleave precursors of the proinflammatory cytokines IL-1β and IL-18. Secretion of mature IL-1β and IL-18 helps to orchestrate the inflammatory response to infection. The magnitude and timing of the inflammatory response must be controlled to limit damage to bystander cells. Inflammasome-mediated signaling has varying affects during CNS infections (Prow and Irani, 2008; Sergerie et al., 2007; Liang et al., 1999). Inflammasome activation during WNV infection is protective, as mice deficient in inflammasome components have increased virus replication in the brain and decreased survival (Kumar et al., 2013; Ramos et al., 2012).

In contrast, inflammasome activation in microglia and astrocytes contributes to increased immunopathology and possibly bystander neuronal death during Japanese encephalitis virus infection (Kaushik et al., 2012; Das et al., 2008).

Neurons are active contributors to the innate immune response during virus infection as has been demonstrated in cultures of primary and immortalized neurons (Schultz et al., 2014; Farmer et al., 2013; Cho et al., 2013a; Peltri et al., 2013; Castorena et al., 2008; Delhaye et al., 2006; Préhaud et al., 2005). In response to alphavirus, flavivirus, and bunyavirus infections, mature neurons rapidly activate IRF-3 and IRF-7 to induce expression of type-I IFN, limit virus replication, and preserve neuronal function (Schultz et al., 2014; Farmer et al., 2013; Peltri et al., 2010; Daffis et al., 2008b; Castorena et al., 2008; Daffis et al., 2007). Additionally, IL-1β synergizes with IFN-β to control WNV replication in neurons (Ramos et al., 2012). The combination and importance of each innate immune signaling pathway in response to infection is likely cell type and virus specific.

In addition to factors that control virus replication, infected cells produce factors that activate astrocytes and microglia, upregulate expression of MHC molecules on microglial cells, increase expression of adhesion molecules including intercellular adhesion molecule 1 and vascular adhesion molecule 1 (VCAM1) on capillary endothelial cells to direct leukocyte infiltration to the site of infection, and modulate the inflammatory response. Cytokines and chemokines important for these processes are induced in a virus-specific manner but often include IFN-γ, IL-1, IL-6, IL-10, IL-12, tumor necrosis factor (TNF), CCL1, CCL2, CCL5, CXCL9, and CXCL10 (Kulcsar et al., 2014; Tun et al., 2014; Lee et al., 2013; Hayasaka et al., 2013; Metcalf et al., 2013; Ramos et al., 2012; Stubblefield Park et al., 2011; Shrestha et al., 2006; Klein et al., 2005; Burdeinick-Kerr and Griffin, 2005; Bergmann et al., 2004; Chang et al., 2000; Liang et al., 1999). These factors facilitate recruitment of circulating leukocytes across the BBB and into the CNS.

**The Adaptive Immune Response**

In addition to controlling virus replication in CNS cells, innate immune signaling initiates the virus-specific adaptive immune response. Infiltration of mononuclear inflammatory cells into the CNS typically begins 3–4 days after infection (Figure 2(b) and 2(c)). T cell and B cell trafficking into the CNS is promoted by neuronal expression of the chemokine CXCL10 that binds to CXCR3 on activated T cell and B cell (Phares et al., 2013; Zhang et al., 2008; Klein et al., 2005). Additionally, proper trafficking of T cells to appropriate brain regions is promoted by signaling...
through CCR5 and CXCR4 (McCandless et al., 2008). Cells first accumulate in the perivascular areas and then infiltrate the parenchyma in the regions of virus infection. Essentially, all components of the cellular immune response are detected in the infiltrate: natural killer (NK) cells, antigen-specific CD4+ and CD8+ T cells, B cells, and monocytes/macrophages (Peña et al., 2014; Zhao et al., 2013; Lee et al., 2013; Chang et al., 2006; Rowell and Griffin, 1999; Parra et al., 1997; Pearce et al., 1994; Wesselingh et al., 1994). The uninfected CNS does not have professional antigen-presenting cells capable of activating naïve T cells, but dendritic cells are detected in the CNS during inflammation after either entering from the circulation or developing from a subpopulation of activated microglia. Presentation of viral peptide antigen in association with the appropriate MHC molecules, predominantly expressed on glial cells, retains activated T cells in the CNS (Kimura and Griffin, 2000; Irani and Griffin, 1996; Suzumura et al., 1988). The continued presence of viral protein antigens promotes long-term retention of virus-specific B cells (Phares et al., 2013; Metcalf et al., 2013).

**Immune-Mediated Virus Clearance**

Virus is cleared from the CNS in a multistep process that must first stop cell-to-cell spread and eliminate cell-free infectious virus (Figure 2(b)). This phase of viral clearance can be assessed by measurement of infectious virus but, as neutralizing antibody is produced, virus clearance is best assessed by quantitative measurement of viral nucleic acid. Initially, local production of type-I IFN reduces cell-to-cell spread through paracrine antiviral signaling. Infectious virus is neutralized by antibody produced by B cells that enter the CNS and interact with viral glycoproteins on the infected cell surface. Additionally, IFN-γ, interacting with IFN-γ receptors expressed on the surfaces of infected cells, inhibits virus production (Phares et al., 2013; Metcalf et al., 2013; Stewart et al., 2011; Hooper et al., 2009; Tschen et al., 2006; Binder and Griffin, 2001; Ulbol et al., 1995; Levine et al., 1991).

For full recovery, virus-infected cells or viral genomes need to be cleared from the CNS. In peripheral tissues, virus-infected cells are usually eliminated by virus-induced or immune-mediated cytolyis. Clearance of virus-infected cells in the CNS becomes a more complicated process due to the nonrenewable and essential nature of neurons and the important role of glial cells in maintaining neuronal function. If the immune system destroys the infected cell, then the outcome of infection will be the same as if the virus caused cell death. However, if infected cells are allowed to survive, there must be a clearance mechanism that inhibits synthesis of viral nucleic acid and proteins and eliminates viral genomes.

If clearance is not complete, mechanisms are needed to avoid progressive or relapsing disease. These processes must be tightly regulated to prevent immune-mediated damage to both infected and uninfected cells during the response to CNS infection. For instance, the CD8+ T cell response can be detrimental during WNV infection (Szretter et al., 2012; Wang et al., 2003). During fatal encephalomyelitis due to infection with a neurovirulent strain of the alphavirus SINV, infiltration of Th1 and Th1/Th17 CD4+ T cells is associated with a rapidly fatal paralytic disease. This response is modulated by IL-10 produced by intrinsic cells of the CNS and by infiltrating regulatory T cells (Kukkar et al., 2014). IL-10 also plays a protective role during coronavirus and flavivirus infections of the CNS (Tu et al., 2014; Hayasaka et al., 2013; Trandem et al., 2011).

**Clearance from Neurons**

Generally, clearance of RNA viruses from neurons occurs through noncytolytic antibody and cytokine-mediated mechanisms to preserve neuronal function. This process has been studied both in virus-infected mice and in cultured neurons. In mice, the clearance of SINV is a two-phase process (Metcalf and Griffin, 2011). Infectious virus is rapidly cleared during the first week after infection and then viral RNA is cleared slowly over the next 30–60 days followed by persistence of a low level of RNA. CD8+ T cells followed by CD4+ T cells and B cells enter the CNS during the first phase when infectious virus is cleared. In the second phase, T cell and B cell are retained in the CNS during viral RNA clearance with overall larger numbers of CD4+ T cells and B cells than CD8+ T cells. Numbers of immune cells in the CNS gradually decrease with decreasing RNA, but the resident populations are steadily enriched in those that are virus specific. Within 2 months after SINV infection, most antibody-secreting cells (ASCs) produce SINV-specific IgG (Metcalf and Griffin, 2011; Tyor et al., 1992).

Antibody that mediates virus clearance from neurons is often directed against viral structural proteins on the infected cell surface and has been most completely analyzed for cells infected with SINV (Hooper et al., 2009; Levine et al., 1991). In addition to neutralizing free virus, antibody to the SINV E2 glycoprotein can bind to the surface of infected cells and may direct intracellular signaling to control virus replication (Després et al., 1995b; Levine and Griffin, 1992). The antiviral effect of this antibody does not require complement or phagocytic cells, but is dependent on bivalent antibody, implying that cross-linking of viral proteins at the cell surface results in intracellular inhibition of virus production (Ubol et al., 1995; Levine et al., 1991). Antibody acts by unknown mechanisms to suppress virus replication and restore host protein synthesis, membrane potential, and type-I IFN responsiveness (Després et al., 1995a,b).

CD8+ T cells can exert antiviral effector functions either through a noncytotoxic, cytokine-mediated, or a cytotoxic pathway. The most effective noncytotoxic cytokine identified is IFN-γ and the cytotoxic effector pathways involve perforin and granzymes or CD95 (Fas)–CD95L interaction. CD8+ T cells can be activated by interactions with MHC class I complexes on neurons (Chevalier et al., 2011) or through cross-priming interactions with MHC class I molecules on surrounding glial cells. T cells recruited into the CNS during SINV infection facilitate but are not necessary, for RNA clearance (Rowell and Griffin, 2002; Kimura and Griffin, 2000). IFN-γ alone can clear SINV from motor neurons, but not from cortical or hippocampal neurons which require antibody (Burdeinick-Kerr and Griffin, 2005; Binder and Griffin, 2001). IFN-γ production by T cells is also important for clearance of MHV, Borna disease virus, and measles virus infections from the CNS (O’Donnell et al., 2012; Stubblefield Park et al., 2014; Metcalf et al., 2013).
In orchestrating T cell infiltration during acute infection by IFN-γ and CCL5 and their receptors CCR1, CCR5, and CXCR3 by microglial cells, cytotoxic T cells are targeted to infected neurons upon upregulation of protease molecules (Fas or TRAIL ligand) and increased MHC class I expression (Shrestha et al., 2012; Chevalier et al., 2011; Shrestha and Diamond, 2007). Neurons infected with virulent strains of rabies virus upregulate Fasl and B7-H1 to inhibit T cell function and prevent virus clearance and the virus-induced inflammatory response (Lafon et al., 2008; Baloul et al., 2004). Additional upregulation of the nonclassical MHC class I molecule HLA-G on infected neurons may promote tolerance (Lafon et al., 2005).

**Clearance from Glial Cells**

The best-studied examples of glial cell infections in mice are the picornavirus TMEV and coronavirus MHV. Failure to clear the acute infection by susceptible strains of mice leads to persistent production of infectious virus and immune-mediated demyelinating disease. Thus, these infections have become models for the human demyelinating disease multiple sclerosis.

TMEV has an early encephalitic phase, which mainly involves infection of neurons, followed by persistent infection of glial cells. In resistant strains of mice, virus clearance is dependent on a rapid CD8^+ T cell response (Lindsley and Rodriguez, 1989). In susceptible strains, infectious virus is cleared from the neurons, but not from microglia, astrocytes, or oligodendrocytes. Establishment of a persistent infection involves failure of all stages of the immune response, beginning with innate immune signaling through TLR3 and TLR2, proinflammatory molecule expression (IL-6), and regulation of infiltrating T cells (Jin et al., 2010; So and Kim, 2009). IL-6 inhibits cytotoxic T cell function and apoptotic death by preferential induction of IL-17-producing Th17 cells (Hou et al., 2009).

Additionally, IL-17 and IL-6 synergistically promote expression of prosurvival Bcl family members that facilitate survival of virus-infected cells (Hou et al., 2014).

MHV infects a wide range of cell types including macrophages, microglia, astrocytes, and oligodendrocytes. The early adaptive response to MHV infection is characterized by expression of the chemokines CXCL9, CXCL10, CCL2, CCL3, and CCL5 and their receptors CCR1, CCR5, and CXCR3 by microglia and astrocytes (Lane et al., 1998). CXCL10 expression is important for recruitment of T cells (Phares et al., 2013). Proinflammatory cytokine expression (i.e., IL-1α/β, IL-6, and IFN-β) decreases as the percentage of virus-specific CD8^+ T cells and expression of T cell support molecules (i.e., CXCL10, CCL5, and IFN-γ) increases (Lane et al., 1998; Parra et al., 1997). IFN-γ plays a key role in dampening MHV replication and orchestrating T cell infiltration, along with maximal expression of MHC molecules on microglia and macrophages (Whitman et al., 2009; Bergmann et al., 2004, 2003; Parra et al., 1997). Infiltrating CD4^+ T cells accumulate around blood vessels and provide supporting factors for infiltrating CD8^+ T cells that invade the parenchyma at the site of infection (Phares et al., 2011; Stohlman et al., 1998). Granzyme B-positive CD8^+ T cells target MHC class I–positive, infected cells for cytolysis, but effector function may be specific for the targeted cell type (Ramakrishna et al., 2004; Lin et al., 1997). IFN-γ is particularly important for clearance from oligodendrocytes, whereas perforin and CD8^+ T cell–mediated cytolysis is important for the clearance of virus from astrocytes and microglia (González et al., 2005; Bergmann et al., 2003; Parra et al., 1999; Lin et al., 1997; Stohlman et al., 1995). Oligodendrocyte killing by CD8^+ T cells results in demyelination during the acute phase of infection (Templeton and Perlman, 2008). Cytolytic function declines concomitantly with loss of viral antigen (Ramakrishna et al., 2004; Lin et al., 1999). Viral RNA persists within the CNS for over 12 months, regardless of the presence of nonanergic, virus-specific CD4^+ and CD8^+ T cells retained in the CNS (Phares et al., 2011, 2010; Ramakrishna et al., 2004; Bergmann et al., 1999). Additionally, persistent oligodendrocyte infection and the consequent immune response are associated with chronic demyelination.

Long-term control by MHV infection (Figure 2c), regardless of infected cell type, is characterized by virus-specific antibody, a lack of infectious virus, and low levels of viral RNA that are detected by sensitive methods such as qPCR (Metcalf and Griffin, 2011; Stewart et al., 2011; Appler et al., 2010; Fragoudis et al., 2008; Tschen et al., 2002; Tzir et al., 1992). Although control of the acute phase of MHV infection by the adaptive response is independent of antibody, long-term production of antibody is necessary to prevent reactivation of infection (Ramakrishna et al., 2002; Lin et al., 1999). As the BBB does not allow antibody to efficiently enter the CNS from the periphery, ASCs must either be continuously recruited to the CNS or maintained in the brain parenchyma to produce antibody locally (Metcalf et al., 2013; Stewart et al., 2011; Hooper et al., 2009; Diamond, 2003; Diamond et al., 2003; Ramakrishna et al., 2002; Tzir et al., 1992; Levine and Griffin, 1992; Parsons, 1989). Antibody controls persistent infection in the CNS through a multifaceted defense strategy that preserves neuronal function following infection. The need for continued antibody production in the CNS is highlighted in studies where passive transfer of antibody blocked recrudescence only during the time of treatment (Ramakrishna et al., 2002; Levine and Griffin, 1992; Levine et al., 1991).

Molecular cues in the brain microenvironment orchestrate ASC recruitment, retention, and maturation. ASCs remain in the CNS to block reactivation of virus replication. The mechanisms for recruitment and retention have been characterized during MHV and SINV infection (Metcalf and Griffin, 2011; Marques et al., 2011; Lin et al., 1999; Tzir and Griffin, 1993). The chemokine receptor CXCR3 and its ligand CXCL10 are critical for recruitment of ASCs to the CNS during MHV infection (Phares et al., 2013; Gil-Cruz and Perez-Shibayama, 2012; Marques et al., 2011). CXCL10 is also elevated during SINV, TMEV, and rabies virus infections, although its role in ASC recruitment has not been defined (Rainey-Barger et al., 2011; Kuang et al., 2009; Phares et al., 2006; Hoffman et al., 1999).
Infiltrating B cells early in infection are naïve/early activated but progress to a more differentiated, isotype-switched phenotype. Consequently, ASC that first enter the CNS produce IgM, likely contributing to neutralization of free virus. Through the course of infection, IgG predominates with IgA also present and declining levels of IgM (Phares et al., 2014; Metcalfe and Griffin, 2011; Tschien et al., 2002; Tyror and Griffin, 1993). Long-term expression of B cell activating factor (BAFF) and a proliferating-inducing ligand (APRIL) in the brain likely support ASC survival (Metcalfe et al., 2013; Metcalfe and Griffin, 2011; Phares et al., 2011; Tschien et al., 2006).

CD4+ and CD8+ T cells are also retained in the CNS after virus infection (Metcalfe and Griffin, 2011; Stewart et al., 2011; Wakim et al., 2010). Antigen-mediated upregulation of the adhesion molecule CD103 on infiltrating effector CD8+ T cells leads to prolonged retention of T cell clusters after infection (Wakim et al., 2010). Together, B cells and T cells retained in the CNS after infection suppress reactivation of virus replication by residual viral RNA.

References

Apper, K.K., Brown, A.N., Stewart, B.S., Behr, M.J., 2010. Persistence of West Nile virus in the central nervous system and periphery of mice. PLoS One 5 (5).

Baloul, L., Camelo, S., Lafon, M., 2004. Up-regulation of fas ligand (FasL) in the central nervous system: a mechanism of immune evasion by rhabdoviruses. J. Neurovirol. 10 (6), 372–382.

Barnett, E.M., Perlman, S., 1993. The olfactory nerve and not the trigeminal nerve is the major site of CNS entry for mouse hepatitis virus, strain JHM. Virology 194 (1).

Bennett, R.S., Cress, C.M., Ward, J.M., Firestone, C.-Y., Murphy, B.R., Whitehead, S.S., 2008. La Crosse virus infectivity, pathogenesis, and immunogenicity in mice and monkeys. Virology 378 (1), 464–472.

Bergmann, C.C., Altman, J.D., Hinton, D., Stohlman, S.A., 1999. Inverted immunol. 195 (1–2), 51–56.

Bergmann, C.C., Park, H., Hinton, D.R., Chandran, R., Montoro, M., Stohlman, S.A., 2003. Perforin-mediated effector function within the central nervous system requires IFN–mediated MHC up-regulation. J. Immunol. 170 (6), 3204–3213.

Bergmann, C.C., Park, H., Hinton, D.R., Chandran, R., Montoro, M., Stohlman, S.A., 2004. Perforin and gamma interferon-mediated control of coronavirus central nervous system infection by CD8 T cells in the absence of CD4 T cells. J. Virol. 78 (4), 1739–1750.

Binder, G.K., Griffin, D.E., 2001. Interferon-gamma-mediated site-specific clearance of alphavirus from CNS neurons. Science (New York, NY) 293 (5528), 303–306.

Burdeinick-Kerr, R., Griffin, D.E., 2005. Gamma interferon-dependent, noncytolytic clearance of sindbis virus infection from neurons in vitro. J. Virol. 79 (9), 5374–5385.

Byrne, J.J., Griffin, D.E., 2000. Control of sindbis virus infection by antibody in interferon-deficient mice. J. Virol. 74 (8), 3905–3908.

Castorona, K.M., Pettier, D.C., Peng, W., Miller, D.J., 2008. Maturating-dependent responses of human neuronal cells to western equine encephalitis virus infection and type I interferons. Virology 372 (1), 208–220.

Chakraborty, S., Nuzmi, A., Dutta, K., Basu, A., 2010. Neurons versus viral attack: victims or warriors? Neurochem. Int. 56 (6–7), 727–735.

Chang, J., Zaczynska, E., Katsev, D., Platsoucas, C.D., Oleszak, E.L., 2000. Differential expression of TGF-β, IL-2, and other cytokines in the CNS of Thielers’s murine encephalomyelitis virus-infected susceptible and resistant strains of mice. Virology 278 (2), 346–360.

Charles, P.C., Walters, E., Margolis, F., Johnston, R.E., 1995. Mechanism of neuro-invasion of venezuelan equine encephalitis virus in the mouse. Virology 208 (2), 662–671.

Chavarría, A., Cárdenas, G., 2013. Neuronal influence behind the central nervous system regulation of the immune cells. Front. Integr. Neurosci. 7.

Chevalier, S., Huberli, E., Montet, C., Duplan, V., Martin-Blandel, G., Famiggia, F., et al., 2011. Neurons are MHC class I-dependent targets for CD8 T cells upon neurotropic viral infection. PLoS Pathog. 7 (11), e1002393.

Cho, H., Proll, S.C., Sztetter, K.J., Katz, M.G., Gale, M., Diamond, M.S., 2013a. Differential innate immune response programs in neuronal subtypes determine susceptibility to infection in the brain by protein-based RNA viruses. Nat. Med. 19 (4), 458–464.

Cho, H., Shrestha, B., Sen, G.C., Diamond, M.S., 2013b. A role for Ilt2 in restricting West Nile virus infection in the brain. J. Virol. 87 (15).

Chung, K., Wallace, J., Kim, S.Y., Kalyanasundaram, S., 2013. Structural and molecular interrogation of intact biological systems. Nature 497, 332–337.

Daffis, S., Samuel, M.A., Keller, B.C., Gale, M., Diamond, M.S., 2007. Cell-specific IRF-3 responses protect against West Nile virus infection by interferon-dependent and -independent mechanisms. PLoS Pathog. 3 (7), e1001261.

Daffis, S., Samuel, M.A., Suthar, M.S., Gale, M., Diamond, M.S., 2008a. Toll-like receptor 3 has a protective role against West Nile virus infection. J. Virol. 82 (21), 10349–10358.

Daffis, S., Samuel, M.A., Suthar, M.S., Keller, B.C., Gale, M., Diamond, M.S., 2008b. Interferon regulatory factor IRF-7 induces the antiviral alpha interferon response and protects against lethal West Nile virus infection. J. Virol. 82 (17), 8465–8475.

Delehaye, S., Paul, S., Blakogor, G., Minet, M., Weber, F., Staeheli, P., et al., 2006. Neurons produce type I interferon during viral encephalitis. Proc. Natl. Acad. Sci. U.S.A. 103 (20), 7835–7840.

Després, P., Griffin, J.W., Griffin, D.E., 1995a. Antiviral activity of alpha interferon in sindbis virus-infected cells is restored by anti-E2 monoclonal antibody treatment. J. Virol. 69 (11), 7345–7348.

Després, P., Griffin, J.W., Griffin, D.E., 1999b. Effects of anti-E2 monoclonal antibody on sindbis virus replication in AT3 cells expressing Bcl-2. J. Virol. 69 (11), 7000–7014.

Diamond, M.S., 2003. A critical role for induced IgM in the Protection against West Nile virus infection. J. Exp. Med. 198 (12), 1853–1862.

Diamond, M.S., Gale, M., 2012. Cell-intrinsic innate immune control of West Nile virus infection. Trends Immunol. 33 (10), 522–530.

Diamond, M.S., Shrestha, B., Marri, A., Mahan, D., Engle, M., 2003. B cells and antibody play critical roles in the immediate defense of disseminated infection by West Nile encephalitis virus. J. Virol. 77 (4), 2578–2586.

Durrant, D.M., Robinette, M.L., Klein, R.S., 2013. IL-1R1 is required for dendritic cell-mediated T cell reactivation within the CNS during West Nile virus encephalitis. J. Exp. Med. 210 (3), 503–516.

Dua, S., Mishra, M.K., Gnoth, J., Basu, A., 2008. Japanese encephalitis virus infection induces IL-18 and IL-1-beta in microglia and astrocytes: correlation with in vitro cytokine responsiveness of glial cells and subsequent neuronal death. J. Neuroimmunol. 195 (1–2), 60–72.

Elmer, B.M., McAllister, A.K., 2012. Major histocompatibility complex class I proteins in brain development and plasticity. Trends Neurosci. 35 (11), 660–670.

Fahy, Z., Topham, D.J., Fee, D., Herkin, J., Carlino, J.A., Hart, M.N., et al., 1996. TGF-Beta 2 decreases migration of lymphocytes in vitro and homing of cells into the central nervous system in vivo. J. Immunol. 155 (1), 325–332.

Farmer, J.R., Altshlafter, K.M., O’Shea, K.S., Miller, D.J., 2013. Activation of the type I interferon pathway is enhanced in response to human neuronal differentiation (Vasilakis, N., Ed.). PLoS One 8 (3), e58813.

Finley, K.H., Longshore, W.A., Palmer, R.J., Cook, R.E., 1955. Western equine and St. Louis encephalitis preliminary report of a clinical follow-up study in California. Neurology 5, 223–235.
Johnson, M.D., Gold, L.I., Moses, H.L., 1992. Evidence for transforming growth factor-

Kimura, T., Griffith, J., Jin, Y.H., Hou, W., Kim, S.J., Fuller, A.C., Kang, B., 2010. Type I interferon signals

Jackson, A.C., Rossiter, J.P., Lafon, M., 2006. Expression of toll-like receptor 3 in the

Hou, W., Jin, Y.H., Kang, H.S., Kim, B.S., 2014. Interleukin-6 (IL-6) and IL-17

Hoffman, L.M., Fife, B.T., Begolka, W.S., 1999. Central nervous system chemokine

Hoek, R.M., Ruuls, S.R., Murphy, C.A., Wright, G.J., 2000. Down-regulation of the

Irani, D.N., Griffith, J., Jin, Y.H., Hou, W., et al., 2013. TNF-

Hayasaka, D., Shirai, K., Aoki, K., Nagata, N., Simantini, D.S., Kitaura, K., et al., 2013. TNF-

Hart, J., Tillman, G., Kraut, M.A., Chiang, H.S., 2014. West Nile virus neuroinvasive

Gil-Cruz, C., Perez-Shibayama, C., 2012. T Helper cell-and CD40-dependent germline

Frolov, I., Akhrymuk, M., Akhrymuk, I., Atasheva, S., Frolova, E.I., 2012. Early events in alphavirus replication determine the outcome of infection. J. Virol. 86 (9), 5055–5066.

F disclosed financial relationships with Alexion Pharmaceuticals andライブラリーアクセスに失敗しました。
Nallat, S.C., Kalvakolanu, D.V., 2014. Interferons, signal transduction pathways, and the central nervous system. J. Interferon Cytokine Res. 34 (8), 559–576.
Neal, J.W., 2014. Flaviviruses are neurotropic, but how do they invade the CNS? J. Infect. 69 (3), 203–215.
Doi, M.H., Lewithwaite, P., Lai, B.F., Mohan, A., Clear, D., Lim, L., et al., 2008. The epidemiology, clinical features, and long-term prognosis of japanese encephalitis in central sarawak, Malaysia, 1997-2005. Clin. Infect. Dis. 47 (4), 458–469.
O’Donnell, L.A., Conway, S., Rose, R.W., Nicolas, E., Slifker, M., Balachandran, S., et al., 2012. STAT1-independent control of a neurotropic measles virus Challenge in primary neurons and infected mice. J. Immunol. (Baltimore, Md: 1950) 188 (4), 1915–1923.
Parsons, L.M., Webb, H.E., 1989. Identification of immunoglobulin-containing cells in the central nervous system of the mouse following infection with the demyelinating strain of Semliki forest virus. Br. J. Exp. Pathol. 70 (3), 247.
Parra, B., Hinton, D.R., Marten, N.W., Bergmann, C.C., Lin, M.T., Yang, C.S., et al., 1997. Kinetics of cytokine mRNA expression in the central nervous system following lethal and nonlethal coronavirus-induced acute encephalomyelitis. Virology 233 (2), 260–270.
Parra, B., Hinton, D.R., Marten, N.W., Bergmann, C.C., Lin, M.T., Yang, C.S., et al., 1999. IFN-γ is required for viral clearance from central nervous system oligodendroglia. J. Immunol. 162 (3), 1641–1647.
Pearce, B.D., Hobbs, M.V., McGraw, T.S., Buchmeier, M.J., 1994. Cytokine induction during T-cell-mediated clearance of mouse hepatitis virus from neurons in vivo. J. Virol. 68 (9), 5483–5495.
Pettier, D.C., Lazear, H.M., Farmer, J.R., Diamond, M.S., Miller, D.J., 2013. Neurotropic arboviruses induce interferon regulatory factor 3-mediated neuronal responses that are cytotoxic, interferon independent, and inhibited by western equine encephalitis virus capsid. J. Virol. 87 (3), 1821–1833.
Pettier, D.C., Simms, A., Farmer, J.R., Miller, D.J., 2010. Human neuronal cells possess functional cytoplasmic and TLR-mediated innate immune pathways influenced by phosphatidylinositol-3 kinase signaling. J. Immunol. (Baltimore, Md: 1950) 184 (12), 7010–7021.
Péjja, J., Plante, J.A., Carillo, A.C., Roberts, K.K., Cua, D.J., Stohlman, S.A., et al., 2014. Multiplexed digital mRNA profiling of the inflammatory response in the West Nile virus flavivirus mouse model (Williams, M., Ed.), PloS Neglected Trop. Dis. 8 (10), e3216.
Phares, T.W., DiSano, K.D., Stohlman, S.A., Bergmann, C.C., 2014. Progression from IgD⁺ IgM⁺ to isotype-switched B cells is site specific during coronavirus-induced encephalomyelitis. J. Virol. 88 (16), 8683–8687.
Phares, T.W., Koo, R.S., Mikhailova, T., Hooper, D.C., 2006. Regional differences in blood-brain barrier permeability changes and inflammation in the apathogenic clearance of virus from the central nervous system. J. Immunol. 176 (12), 7666–7675.
Phares, T.W., Marques, C.P., Stohlman, S.A., Hinton, D.R., Bergmann, C.C., 2011. Factors supporting intrathecal humoral responses following viral encephalomyelitis. J. Virol. 85 (5), 2593–2598.
Phares, T.W., Stohlman, S.A., Hinton, D.R., Bergmann, C.C., 2013. Astrocyte-derived CXCL10 drives accumulation of antibody-secreting cells in the central nervous system during viral encephalomyelitis. J. Virol. 87 (6), 3382–3392.
Phares, T.W., Stohlman, S.A., Hinton, D.R., Atkinson, R., Bergmann, C.C., 2010. Enhanced antiviral T cell function in the absence of IFN-γH is insufficient to prevent persistence but exacerbates aconal bystander damage during viral encephalomyelitis. J. Immunol. (Baltimore, Md: 1950) 185 (9), 5007–5018.
Phillips, A.T., Stauft, C.B., Aboellail, T.A., Toth, A.M., Jarvis, D.L., Powers, A.M., et al., 2013. Bioluminescent imaging and histopathologic characterization of West Nile virus infection in mice. J. Virol. 87 (17), 12259–12269.
Phares, T.W., Stohlman, S.A., Hinton, D.R., Bergmann, C.C., 2010. Enhanced T cell function in the absence of IFN-γH is insufficient to prevent persistence but exacerbates aconal bystander damage during viral encephalomyelitis. J. Immunol. (Baltimore, Md: 1950) 180 (6), 3053–3060.
Shrestha, B., Diamond, M.S., 2007. Foxp3 and interleukin–1β play a crucial role in the resistance against lethal herpes simplex virus encephalitis. J. Infect. Dis. 196 (10), 1549–1555.
Shrestha, B., Stohlman, S.A., Hinton, D.R., Bergmann, C.C., 2010. Enhanced antiviral T cell function in the absence of IFN-γH is insufficient to prevent persistence but exacerbates aconal bystander damage during viral encephalomyelitis. J. Immunol. (Baltimore, Md: 1950) 180 (6), 3053–3060.
Shrestha, B., Wang, T., Samuell, M.A., Whitby, K., Craft, J., Fikrig, E., et al., 2006. Gamma interferon plays a crucial early antiviral role in protection against West Nile virus infection. J. Virol. 80 (11), 5338–5348.
Silverman, M.A., Misasi, J., Smole, S., Feldman, H.A., Cohen, A.B., Santagata, S., et al., 2013. Eastern equine encephalitis in children, Massachusetts and New Hampshire, USA, 1970-2015. Emerging Infect. Dis. 19 (2), 194–201.
Sleti, E., Mccandless, E.E., Klein, R.S., Diamond, M.S., 2007. CD40-CD40 ligand interactions promote trafficking of CD8+ T cells into the brain and protection against West Nile virus encephalitis. J. Virol. 81 (21), 11749–11757.
Sleti, E., Mccandless, E.E., Klein, R.S., Diamond, M.S., 2007. CD40-CD40 ligand interactions promote trafficking of CD8+ T cells into the brain and protection against West Nile virus encephalitis. J. Virol. 81 (21), 11749–11757.
Stewart, B.S., Demarest, V.L., Wong, S.J., Green, S., Bernard, K.A., 2011. Persistence of virus-specific immune responses in the central nervous system of mice after West Nile virus infection. BMC Immunol. 12 (1), 6.
Stohlman, S.A., Bergmann, C.C., Lin, M.T., Cua, D.J., Hinton, D.R., 1998. CTL effector function within the central nervous system requires CD8+ T cells. J. Immunol. 160 (6), 2986–2994.

Ramakrishna, C., Stohlman, S.A., Atkinson, R.A., Hinton, D.R., Bergmann, C.C., 2004. Differential regulation of primary and secondary CD8⁺ T cells in the central nervous system. J. Immunol. 173 (10), 6265–6273.
Stohlman, S.A., Bergmann, C.C., Van Der Veen, R.C., Hinton, D.R., 1995. Mouse hepatitis virus-specific cytotoxic T lymphocytes protect from lethal infection without eliminating virus from the central nervous system. J. Virol. 69 (2), 684–694.

Stubblefield Park, S.R., Widness, M., Levine, A.D., Patterson, C.E., 2011. T cell-, interleukin-12-, and gamma interferon-driven viral clearance in measles virus-infected brain tissue. J. Virol. 85 (7), 3664–3676.

Szretter, K.J., Daniels, B.P., Cho, H., Gainey, M.D., Yokoyama, W.M., Gale, M., et al., 2008. Role of IFN-α and -γ in elimination of virus from the central nervous system. J. Virol. 82 (21), 11421–11431.

Templeton, S.P., Perlman, S., 2008. Role of IFN-γ responsiveness in CD8 T cell-mediated viral clearance and demyelination in coronavirus-infected mice. J. Neuroimmunol. 194 (1–2), 18–26.

Trandem, K., Jin, Q., Weiss, K.A., James, B.R., Zhao, J., Perlman, S., 2011. Virally expressed interleukin-10 ameliorates acute encephalomyelitis and chronic demyelination in coronavirus-infected mice. J. Virol. 85 (14), 6822–6831.

Tschen, S.I., Bergmann, C.C., Ramakrishna, C., Morales, S., Atkinson, R.D., Stohlman, S.A., 2002. Recruitment kinetics and composition of antibody-secreting cells within the central nervous system following viral encephalomyelitis. J. Neuroimmunol. 136 (1–2), 2922–2929.

Tschen, S.I., Stohlman, S.A., Ramakrishna, C., Hinton, D.R., Atkinson, R.D., Bergmann, C.C., 2006. CNS viral infection diverts homing of antibody-secreting cells from lymphoid organs to the CNS. Eur. J. Immunol. 36 (3), 603–612.

Tun, M.M.N., Aoki, K., Senba, M., Bueno, G.C., Shirai, K., Suzuki, R., et al., 2014. Protective role of TNFα, IL-10 and IL-2 in mice infected with the Oshima strain of Tick-borne encephalitis virus. Sci. Rep. 4, 3544.

Tyr, W.R., Griffin, D.E., 1993. Virus specificity and isotype expression of intraparenchymal antibody-secreting cells during sindbis virus encephalitis in mice. J. Neuroimmunol. 48 (1), 37–44.

Tyr, W.R., Wesselingh, S., Levine, B., Griffin, D.E., 1992. Long term intraparenchymal IgG secretion after acute viral encephalitis in mice. J. Immunol. 149 (12), 4016–4020.

Uboi, S., Levine, B., Lee, S.H., Greenspan, N.S., Griffin, D.E., 1995. Roles of immunoglobulin valency and the heavy-chain constant domain in antibody-mediated downregulation of sindbis virus replication in persistently infected neurons. J. Virol. 69 (3), 1990–1993.

Wakim, L.M., Woodward-Davis, A., Bevan, M.J., 2010. Memory T cells persisting within the brain after local infection show functional adaptations to their tissue of residence. Proc. Natl. Acad. Sci. U.S.A. 107 (42), 17872–17879.

Wang, Y., Lobigs, M., Lee, E., Mullbacher, A., 2003. CD8+ T cells mediate recovery and immunopathology in West Nile virus encephalitis. J. Virol. 77 (24), 13323–13334.

Wekerle, H., Engelhardt, B., Risau, W., Meyermann, R., 1991. Interaction of T Lymphocytes with cerebral endothelial cells in vitro. Brain Pathol. 1 (2), 107–114.

Wekerle, H., Lintonning, C., Laissmann, H., 1986. Cellular immune reactivity within the CNS. Trends Neurosci. 9, 271–277.

Wesselingh, S.L., Levine, B., Fox, R.J., Choi, S., Griffin, D.E., 1994. Intracerebral cytokine mRNA expression during fatal and nonfatal alphavirus encephalitis suggests a predominant type 2 T cell response. J. Immunol. 152 (3), 1289–1297.

Whitman, L., Zhou, H., Perlman, S., Lane, T.E., 2009. IFN-γ-mediated suppression of coronavirus replication in glial-committed progenitor cells. Virology 384 (1), 209–215.

Wilson, E.H., Weninger, W., Hunter, C.A., 2010. Trafficking of immune cells in the central nervous system. J. Clin. Invest. 120 (5), 1368–1379.

Wilson, M.R., 2013. Emerging viral infections. Curr. Opin. Neurol. 26 (3), 301–306.

Yamada, M., Nakamura, K., Yoshii, M., Kaku, Y., Namba, M., 2009. Brain lesions induced by experimental intranasal infection of japanese encephalitis virus in piglets. J. Comp. Pathol. 141 (2–3), 156–162.

Yang, B., Trecas, J.B., Kulkarni, R.P., Dewerman, B.E., Olen, C.K., Lubeck, E., et al., 2014. Single-cell phenotyping within transparent intact tissue through whole-body clearing. Cell 158 (4), 945–958.

Zhang, B., Chua, Y.K., Lu, B., Diamond, M.S., Klein, R.S., 2008. CXCR3 mediates region-specific antiviral T cell trafficking within the central nervous system during West Nile virus encephalitis. J. Immunol. 180 (4), 2641–2649.

Zhao, P., Yang, Y., Feng, H., Zhao, L., Qin, J., Zhang, T., et al., 2013. Global gene expression changes in BV2 microglial cell line during rabies virus infection. Infect. Genet. Evol. 20 (C), 257–269.

Zhao, P., Zhao, L., Zhang, T., Qi, Y., Wang, T., Liu, K., et al., 2011. Innate immune response gene expression profiles in central nervous system of mice infected with rabies virus. Comp. Immunol. Microbiol. Infect. Dis. 34 (6), 503–512.