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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.

Microglial cell Bone marrow–derived macrophage lineage glial cell that is the resident 'macrophage' of the CNS. They constantly survey the CNS and become immunologically active upon pathogen detection.

Neuron Electrically active cell that transmits signals from the periphery and within the central nervous system.

Oligodendrocyte Glial cell that produces the myelin sheath around neuronal axons and promotes conduction.

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.

Table 1 Examples of important RNA viruses that infect the CNS

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

[a]Commonly used in mouse models of viral encephalitis.

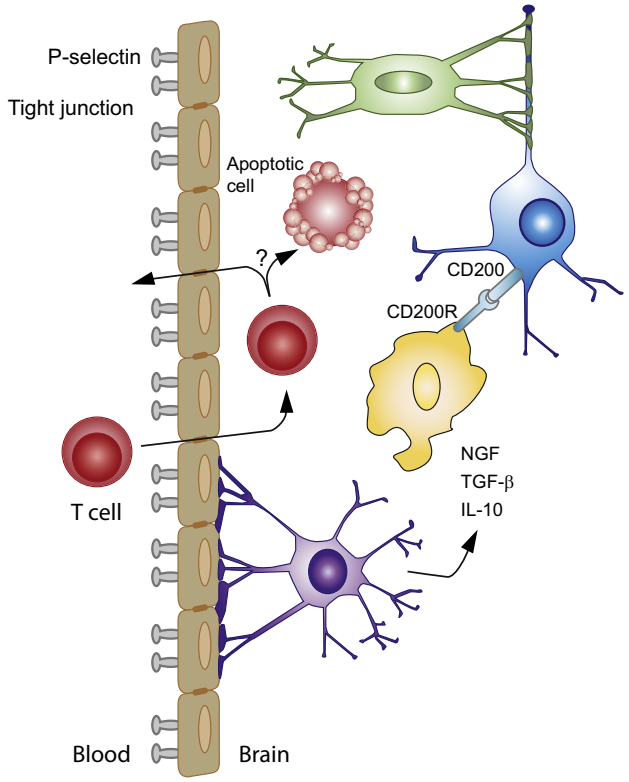
Entry into the CNS

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 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., 2014; O'Donnell et al., 2012; Chakraborty et al., 2010; Daffis et al., 2008a; Castorena et al., 2008; Daffis et al., 2007;



Oligodendrocyte: Glial cell that produces the myelin sheath around neuronal axons and promotes conduction

Neuron: Electrically active cell that transmits signals from the periphery and within the CNS

Microglial cell: Bone marrow–derived macrophage-lineage glial cell that is the resident 'macrophage' of the CNS; constantly surveys the CNS and becomes immunologically active upon pathogen detection

Astrocyte: Glial cell that secretes neuroprotective factors and is associated with maintenance of the BBB

Blood Brain Barrier (BBB): Endothelial cells connected by tight junctions that form a highly selective barrier between the circulating blood and the CNS parenchyma

Figure 1 Important cells in the uninfected brain.

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

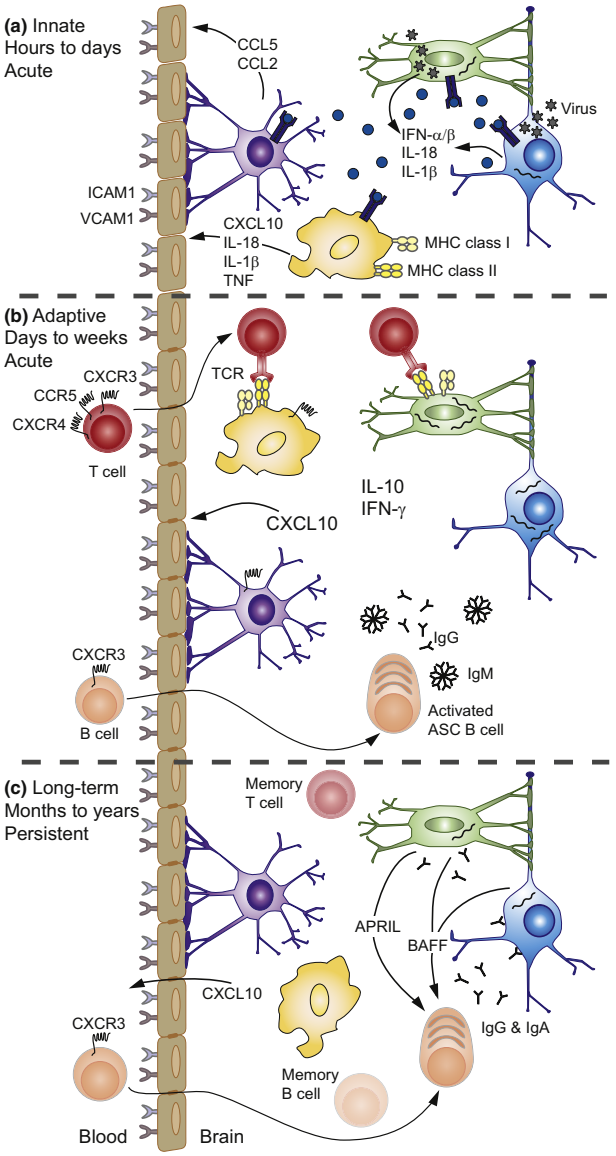


Figure 2 The immune response to virus infections in the Central Nervous System (CNS). The immune response following SINV infection of neurons or MHV infection of oligodendrocytes is shown. (a) The innate immune response controls intracellular virus replication and spread. (b) Lymphocytes from the periphery infiltrate the CNS during the adaptive response to clear infectious virus and block intracellular replication. (c) Long-term retention of virus-specific B cell and T cell blocks recrudescence. APRIL, a proliferating-inducing ligand; BAFF, B cell activating factor.

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 Ifit2 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; Peltier 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; Peltier 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., 2000; 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; Ubol 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 cytolysis. 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 (Kulcsar et al., 2014). IL-10 also plays a protective role during coronavirus and flavivirus infections of the CNS (Tun 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.,

2011; Richter et al., 2009; Templeton and Perlman, 2008; Pearce et al., 1994).

Clearance of WNV is dependent on $CD8^+$ T cells and monocytes, not antibody (Sitati et al., 2007; Shrestha et al., 2006; Klein et al., 2005). Monocyte-derived cells likely signal to T cells, leading to optimal activation necessary for virus clearance (Durrant et al., 2013). T cells clear virus through IFN-γ production or through cytotoxic methods, such as perforin (Shrestha et al., 2006). Cytotoxic T cells are targeted to infected neurons upon upregulation of prodeath 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 concomitant 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

Long-term control of virus infection (**Figure 2(c)**), 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; Fragkoudis et al., 2008; Tschen et al., 2002; Tyor 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; Tyor 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; Tyor 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; Metcalf and Griffin, 2011; Tschen et al., 2002; Tyor 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 (Metcalf et al., 2013; Metcalf and Griffin, 2011; Phares et al., 2011; Tschen et al., 2006).

$CD4^+$ and $CD8^+$ T cells are also retained in the CNS after virus infection (Metcalf 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.

See also: **Anatomy and Microanatomy of the Immune System:** Central Nervous System: Microanatomy; Roles of Chemokines in Immune Cell Trafficking to Lymphoid Tissues. **B Cell Activation:** Cytokine Regulation of B Cell Activation and Differentiation. **Cytokines and Their Receptors:** IL-10; Interferon γ: An Overview of Its Functions in Health and Disease; Interferon α/β; Viral Anticytokine Strategies. **Development of T Cells and Innate Lymphoid Cells:** CD4/CD8 Lineage Commitment. **Immunity to Viral Infections:** Innate Cytokine Responses and Their Functions during Viral Infections; Protective and Pathogenic T Cell Responses to Virus Infections; T Cell Responses during Acute Respiratory Virus Infection. **Myeloid and B Cell Development:** BAFF and B Cell Development, Homeostasis, and Selection. **Signal Transduction:** Jak-STAT Signaling Pathways; Signaling Pathways Downstream of TLRs and IL-1 Family Receptors.

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