Innate Immunity in Viral Encephalitis

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Host Recognition of Pathogen Associated Molecular Patterns (PAMPs) and Damage Associated Molecular Patterns (DAMPs)

Viruses trigger host responses by engaging several different families of receptors, both surface and within cells; these receptors recognize generic patterns, and not specific sequences (such as a peptide of viral surface protein or genome). One of the best-known families of these pattern recognition receptors is Toll Like Receptors (TLRs), present on the cell surface or endosomal membrane (Lester and Li 2014). Intracellular RIG-I-Like Receptors (RLRs) having common domains called caspase recruitment domain (CARD), helicase, and NACHT are RIG-I (retinoic acid inducible gene-I), MDA5 (melanoma differentiation associated gene 5), Caterpillar, NOD, NALP, NAIP, and CIIT (Fitzgerald et al. 2014b).

TLR bind a wide range of PAMPs, ranging from peptidoglycans of gram-positive and lipopolysaccharides of gram-negative bacteria (TLR 2 and TLR 4, respectively) to viral genomes dsRNA, ssRNA, and dsDNA (TLR3, 7, and 9, respectively). Signaling through TLR leads to production of IFN-β and proinflammatory cytokines (Trotta et al. 2014; Gay et al. 2014; Kawai and Akira 2011). Few cells in the CNS constitutively express high levels of TLR (Suh et al. 2009).

In neurotropic viral infections, TLR are critical for IFN and cytokine production for Enterovirus-71, Human Immunodeficiency Virus-Encephalitis (HIV-E), Herpes simplex virus-1 (HSV-1), Flaviviruses, Japanese encephalitis virus (JEV), Junin virus, LaCrosse virus, Lymphocytic choriomeningitis virus (LCMV), Rabies,

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Semliki Forest virus (SFV), Sindbis, Theiler's murine encephalomyelitis virus (TMEV), and West Nile virus (WNV) (Han et al. 2014; Fadnis et al. 2013; Nazmi et al. 2014; Cuevas and Ross 2014; Denizot et al. 2012; El-Hage et al. 2011; Furr and Marriott 2012; McKimmie et al. 2005; Neal 2014; Olson and Miller 2004; Sabouri et al. 2014; Szretter et al. 2009; Taylor et al. 2014; Thomas et al. 2014; Wollish et al. 2013; Zhou et al. 2008; Zolini et al. 2014).

TLR signaling may regulate the expression of micro-RNAs including MiR-146 and MiR-155, leading to down-regulation of some inflammatory genes (Aalaei-andabili and Rezaei 2013). MiR-155 may regulate JEV-induced inflammation by controlling Src Homology 2-containing inositol phosphatase-1 (SHIP-1) (Thounaojam et al. 2014b) and MiR-29b targets TNF-α-induced protein 3 (Thounaojam et al. 2014a). However, enhanced production of MiR-155 may lead to BBB dysregulation (Lopez-Ramirez et al. 2014).

RIG-I binds 5′ uncapped single stranded RNA, an essential intermediate in RNA virus replication (Goubau et al. 2014; Hornung et al. 2006). **MDA5**, in contrast, recognizes dsRNA (Wu et al. 2013), and is required for picornavirus responses (Kato et al. 2006). Like TLRs, RIG-I activation leads to activation of a protein variously known as Cardif/IPS-1/MAVS/VISA upstream of IRF3 and NF-kB activation, which transduce the signals with nuclear translocation, leading to the production IFN-β and all the downstream IFN-stimulated genes (ISGs) (Schneider et al. 2014). RIG-I is negatively regulated by a deubiquitinase, USP21 (Fan et al. 2014).

While these pathways have been well documented in many cell types, they may not always "work" in the CNS. For instance, while Vesicular stomatitis virus (VSV) replication is extremely sensitive to the antiviral effect of pretreatment of neurons with IFN-β, VSV infection of dendritic cells rapidly induces IFN, it fails to elicit IFN-β production in neurons (Trottier et al. 2005). The mechanism(s) by which IFNs alter cellular physiology to resist viral infection is distinct in neurons when compared to cell types that have been more frequently studied (D'Agostino et al. 2009a, b; Chesler et al. 2003). VSV also evades cell-autonomous responses through one of many actions of the viral M protein, essentially preventing mRNA export from the nucleus (Faria et al. 2005). In mice, VSV infection elicits IFN-β production by plasmacytoid dendritic cells in peripheral lymphoid compartments (Akira and Hemmi 2003), no detectable IFN-β is made in the CNS during the first week of VSV encephalitis (Trottier et al. 2007). In contrast, both Theiler's encephalomyelitis virus (TMEV) and LaCrosse virus infections led neurons to produce Type I IFN (Delhaye et al. 2006). Both RIG-I and MDA5 are essential to detect and control WNV infection (Carty et al. 2014; Errett et al. 2013).

The Receptor for Advanced Glycation End-products (**RAGE**), an activating receptor, is expressed on many cells including vascular smooth muscle cells, endothelial cells, monocytes, and microglia (Ramasamy et al. 2005). It was originally recognized as a contributor to the inflammation seen in diabetes, and binds, as its name suggests, proteins that have been posttranslationally modified with glucose. Engagement of RAGE by its ligands leads to signal transduction through NF-kB and synthesis of proinflammatory mediators, leading to neuroinflammation and oxidative stress (Tobon-Velasco et al. 2014). Other ligands for the receptor are S100 family proteins, **HMGB1** and insoluble complexes of Aβ peptide, which are released during

tissue damage in arthritis, atherosclerosis, aging, neurodegeneration, pulmonary diseases, sepsis, and ischemia (Chuah et al. 2013; Kang et al. 2014). This has led to the classification of RAGE as a Damage Associated Molecular Pattern (**DAMP**) receptor (Foell et al. 2007). Thus direct or indirect compromise of neurons and parenchymal cells during viral encephalitis leads to the release of HMGB1 (Wang et al. 2006) or S100 that can activate microglia, perivascular macrophages, and pericytes, as well as the microvascular endothelial cells (Jaulmes et al. 2006; Rong et al. 2005). Release of S100 or HMGB1 during VSV encephalitis did not contribute to the production of IFN-β by splenic plasmacytoid dendritic cells, since infusion of soluble RAGE did not suppress the response (Reiss and Schmidt, unpublished data). Thus, the BBB may be disrupted; cells within the CNS will secrete cytokines, chemokines, and other inflammatory mediators. This could be among the first of the sequential waves of innate immunity in response to the viral infection.

Interferon-Induced Antiviral Responses

The initial report of a factor made by cells which inhibited viral replication was made ~50 years ago (Isaacs and Lindenmann 1957). There are three Types of IFN. Type I is more diverse, produced by virtually all cells and includes IFN-α, IFN-β, and IFN-τ. Type II has only one member, IFN-γ; Type III comprises IL-28 and IL-29, a family of IFN-λ proteins (Reid and Charleston 2014; Guayasamin et al. 2014; Hermant and Michiels 2014). IFNs inhibit viral replication by pathways described below, may also lead to neurodegeneration and demyelination through the activation of microglial production of neurotoxins (Owens et al. 2014; Block et al. 2007; Mana et al. 2006).

IFN may also be a beneficial cytokine in LCMV and Lassa fever infections where viral pathogenesis may induce vascular leak (Baccala et al. 2014). In Langat virus and TBE infections, IFN is protective against fatal neurotropic disease (Weber et al. 2014a). In measles infections, neurons express IFN needed for early control (Cavanaugh et al. 2015), but in intranasal VSV infection, astrocytes are the source (Detje et al. 2015). Therefore, the beneficial and pathologic effects of IFNs may depend on the quantity and duration of expression.

Once IFNs have been induced and secreted, these cytokine bind ubiquitously expressed receptors and induce a signal transduction kinase cascade starting with Jaks and STATs, leading to nuclear translocation of phosphorylated STAT complexes that result in gene induction in virtually all cells (Nallar and Kalvakolanu 2014; Ivashkiv and Donlin 2014; Owens et al. 2014). As with most other signal transduction cascades, there are regulatory phosphatases that dampen the IFN-mediated induction, these include S̲uppressors o̲f c̲ytokine s̲ignaling (**SOCS**) and P̲rotein i̲nhibitor of a̲ctivated S̲TAT1 (**PIAS**) proteins. Resveratrol may upregulate SOCS-1, and thus dampen inflammation (Dragone et al. 2014). While the Jak-STAT pathway is predominant, secondary signal transduction pathways are also important for IFN's activity (Ivashkiv and Donlin 2014). Although most of the consequences of IFN binding and signaling are transcriptional, not all of the inductive effects of IFNs require new mRNA production; I will discuss that below.

IFN responses are essential host components of intrinsic and cell autonomous immunity to viral infection. Many viruses block IFN signaling or downstream mediators such as Tick borne flaviviruses and IRF-1 signaling (Robertson et al. 2014). The exact pathways by which IFNs antagonize viral replication required are not yet fully elucidated. New techniques such as silencing are providing insights into the downstream mediators (Diamond and Farzan 2013; Fensterl et al. 2012; Schoggins et al. 2014), as are explorations of specific genes used by some viruses to evade antiviral pathways (Taylor and Mossman 2013) such as HSV γ34.5 (Rosato and Leib 2014) or Rabies P-protein (Wiltzer et al. 2014). JEV modulates SOCS in infected macrophages, inhibiting the production and release of proinflammatory cytokines (Kundu et al. 2013).

Many tumors have been shown to have disabled IFN responses; this has led to the development of several viruses for oncolysis, that is, infection to target tumors but spare normal tissue.

Expression of IFNs may be regulated by cellular **micro-RNAs**, targeting the IFN mRNA for destruction. MiR-548 suppresses IFN-λ1 expression (Li et al. 2013b) and MiR-466I targets IFN-α mRNA (Li et al. 2012), leading to increased viral replication.

Some IFN-stimulated genes (**ISG**) are critical for co-stimulation, antigen processing, and presentation, some for antiviral effects, others contribute to regulation of angiogenesis, cellular apoptosis, or stasis (Xiao et al. 2006), and other physiological processes. Hundreds of IFN-regulated genes have been identified using microarray analysis and functional assays (Schneider et al. 2014; Cho et al. 2013; Schoggins et al. 2014). Traditionally these were studied in isolation, and many antiviral pathways have been well characterized including Mx, PKR, RNAseL, OAS, and IDO. I will focus on a few of the more important antiviral pathways controlled by IFNs.

Inactivation of GTP

The first antiviral IFN-stimulated pathway studied in detail initially for myxovirus (Influenza) infections, **Mx**, was discovered in 1978 by Lindenmann and colleagues; they observed that some mice were spontaneously resistant to influenza virus replication and later showed that Mx had GTPase activity (Lindenmann et al. 1978; Isaacs and Lindenmann 1957; Kochs et al. 1998). Other GTPases including Very Large Inducible GTPase-1 and TGTP/Mg21/IRG-47 are induced by IFNs (Klamp et al. 2003). Guanylate binding proteins are also ISGs. These include GBP-1, a Dynamin superfamily member with GTPase activity (MacMicking 2004).

MxA was induced in HIV and Simian immunodeficiency virus (SIV) infection of the CNS (Singh et al. 2014; Zaritsky et al. 2012), and in Reovirus infections Mx was critical to limit viral replication (Dionne et al. 2011). WNV evades the antiviral activity of MxA (Hoenen et al. 2014). An isoform of MxA may lead to enhanced HSV-1 replication (Ku et al. 2011). There are polymorphisms in the promoter region of human MxA; these may lead to altered gene expression, and thus sensitivity to infections or to resistance to exogenous IFN (Tran Thi Duc et al. 2013).

Inhibition of Protein Synthesis

Probably the best known ISG is triggered when dsRNA, produced during viral infection, activates the kinase **PKR**, phosphorylating and inactivating the translation elongation factor eIF2α, inhibiting the production of new proteins in infected cells. This pathway is important in many neurotropic viral infections including MHV-A59, Sindbis, WNV, VSV, TMEV, and HSV-1 (Kapil et al. 2014; Geiss et al. 2003; Baltzis et al. 2004; Cheng et al. 2005; Gorchakov et al. 2004; Palma et al. 2003; Ryman et al. 2005; Ventoso et al. 2006).

Cellular stress associated with the Unfolded Protein Response, when viral glycoprotein synthesis dysregulates endoplasmic reticulum function, is a DAMP response (Smith 2014; Noack et al. 2014). UPR pathway inactivates eIF2α using two enzymes PERK and GCN2 (Berlanga et al. 2006). Flaviviruses such as JEV and Coronaviruses trigger this alarmin response (Noack et al. 2014).

Viperin/cig5/vig is an ISG and also induced during infection by cytomegalovirus (CMV), JC virus, or VSV, and suppresses synthesis of some viruses (Helbig and Beard 2014). Viperin restricts WNV pathogenesis (Szretter et al. 2011). Inhibition of viral protein synthesis is an effective host response to cripple viral infection.

Recognition, Degradation, and Sequestration of Viral RNA and Viral DNA

Recognition of viral RNA in infected cells involves many different pathways. The substrate of 2′,5′-Oligoadenylate Synthase (**OAS**)-Dependent **RNAseL** is viral dsRNA (Hornung et al. 2014). This pathway is important in the resistance to HSV-1, flaviviruses, LCMV, and VSV infections of the CNS (Bhattacharyya 2014). RNAseL may contribute to the apoptosis of infected cells (Castelli et al. 1998).

Adenosine deaminase which acts on dsRNA (**ADAR1**) is an IFN-γ-inducible antiviral enzyme which may be coupled with the PKR pathway (Taylor et al. 2005). ADAR1 restricts measles infection in the CNS (Ward et al. 2011).

IFN-induction of stress granules (also called **P bodies**) may sequester ADAR1 (John and Samuel 2014). Some viruses Mengovirus, TMEV, WNV, JEV, Measles, and Junin prevent the formation of P bodies; while other viral infections including poliovirus, SFV, MHV-A59, and VSV induce the formation of stress granules (Pattnaik and Dinh 2013; Onomoto et al. 2014). TBEV replication is inhibited by sequestration of vRNA in stress granules (Albornoz et al. 2014).

Another antiviral protein that recognizes and sequesters viral mRNAs is Zinc finger Antiviral protein (Glasker et al. 2014). Zinc has been shown to contribute not only to this antiviral protein, but to other proteases including matrix metalloproteinases (MMPs) and metallothionein necessary for diapedesis (Rink and Haase 2007), for inflammatory cells crossing peripheral capillaries or for breaching the BBB, or for migration of CNS parenchymal cells in response to chemoattractants during viral infection. Zinc contributes to inhibition of polyprotein processing for many Picornaviruses (Krenn et al. 2005).

Stimulator of IFN genes (**STING**) [also known as mediator of IRF3 activation (**MITA**)] is activated by IFN-γ inducible protein 16 (**IFI16**) binding to viral dsDNA and HN200; STING then activates TANK binding kinase-1 (TBK-1) phosphorylation of the transcription factor IRF3, resulting in expression of ISGs (Thompson et al. 2014). MITA/STING is an ER and mitochondrial membrane-bound cytoplasmic sensor for pathogen-induced cyclic dinucleotides (cyclic GMP-AMP); its C-terminal domain recruits TBK1 and IRF3 (Dubensky et al. 2013; Ran et al. 2014). The host enzyme cyclic GMP-AMP synthase, **cGAS** (also called MB21D1), is the DNA and also dsRNA sensor (Hornung et al. 2014; Schoggins et al. 2014). NLRC3 is a negative regulator of STING activation (Zhang et al. 2014). Diffusion of cGAMP to neighboring cells may lead to paracrine cell-autonomous innate immunity (Ablasser et al. 2013).

IFI16 senses and contributes to control of HIV-1 infection (Jakobsen et al. 2013). STING can also bind to reverse transcriptase intermediates of Human T cell leukemia virus (HTLV-1), and with IRF3 and SAMHD1, activate apoptosis (Sze et al. 2013). In many viral infections, there is an arms race between the host's ability to shut down viral replication and the virus inactivating host antiviral pathways; that is observed with HSV-1 ICP0 and US3-PK and STING (Kalamvoki and Roizman 2014). Hepatitis C virus (HCV) NS4B blocks STING activation of TBK-1 (Ding et al. 2013). The Dengue virus (DENV) NS2B/3 protease cleaves STING (Aguirre et al. 2012; Green et al. 2014).

IFN-induced protein with tetratricopeptide repeats (**IFIT**) family proteins contribute to antiviral responses IFIT1 (ISG56), IFIT2 (ISG54), IFIT3 (ISG60), IFIT5 (ISG58) and are regulated by viral infection (Hyde et al. 2014; Zhang et al. 2013b). IFIT1 binds the 5′ capped 2′-*O* unmethylated RNA of JEV inhibiting its replication (Kimura et al. 2013), but VEE mutants evade IFIT1 (Hyde et al. 2014). IFIT2 protects mice from VSV neuropathogenesis (Fensterl et al. 2012) and VSV infection of the peripheral nervous system (Fensterl et al. 2014). Ifit2 is essential for host control of neurotropic Mouse Hepatitis Virus A59 (MHV) (Butchi et al. 2014), EMCV, MHV, and WNV (Fensterl and Sen 2015), and HBV (Pei et al. 2014). IFITM is an IFN-induced membrane associated protein. IFIT3 potentiates antiviral signaling by connecting TBK1 and MAVS (Liu et al. 2011). They have broad-spectrum antiviral activity (Diamond and Farzan 2013). However, some neurotropic RNA viruses including WNV can evade host restriction by IFIT family members (Daffis et al. 2010).

Altered Amino Acid Metabolism

The ISG Indoleamine 2,3-Dioxygenase (**IDO**), a catabolic enzyme for tryptophan, generates kynurenines. IDO may have regulatory effects on T cell activity (Sakurai et al. 2002) and may be neuroprotective or neurotoxic: IDO contributes to alterations in serotonin metabolism, enhances astrocyte viability, but contributes to the formation of toxic quinolinic acid (Campbell et al. 2014).

IDO has antiviral activity against vaccinia virus, HTLV-1, measles, and HSV-1 (Adams et al. 2004; Maloney et al. 2000; Oberdorfer et al. 2003). However, it may be antagonistic to containment of HIV-1 (Miller and Bhardwaj 2013). IFN-induced alterations in amino acid metabolism can suppress infection, but clearly this is a two-edged sword.

Miscellaneous Antiviral ISGs

Although the phosphatase(s) and kinase(s) altered by IFN-β treatment in neurons were not identified, in IFN-β-treated neurons, the posttranslational modification of two of the five VSV proteins was profoundly altered; the M protein was *hyper*-phosphorylated and the P protein, a subunit of the RNA-dependent RNA polymerase, was *hypo*-phosphorylated. M protein lost affinity for the RNP complex, impairing assembly, and the RNA-dependent RNA polymerase activity was altered. Together, these modifications led to inhibition of productive VSV replication in neurons (D'Agostino et al. 2009a, b; D'Agostino and Reiss 2010).

There are many other ISGs that have antiviral activity, although they are less well studied. One of these is ISG12; it contributes to resistance to Sindbis encephalitis (Labrada et al. 2002). ISG12 is a nuclear envelope protein that binds nuclear receptors like peroxisome proliferation activating receptors (PPARs) (Uhrin et al. 2013). Cytokines and chemokines will be discussed below.

Ubiquitinases, Deubiquitinases, ISG15, Sumoylation

Posttranslational modifications of proteins are essential for their activities, their cellular localization, and also their half-life. One regulator of protein lifespan is the proteasome; proteins are targeted for degradation by addition of strings of ubiquitin (**Ub**), polyubiquitin tails, by a series of proteins that recognize the target (E1) bridge that complex (E2) to the ubiquitin ligase (E3). There are also host cellular enzymes capable of stripping Ub from proteins, deubiquitinases (Herrmann et al. 2007).

There are both host-cell beneficial applications of Ub-modification and pro-viral life cycle modifications. Malfunction of this pathway leads to accumulation of proteins that should have been degraded, and can result in neurodegenerative diseases (Atkin and Paulson 2014).

An example of viral-enabling modification is induction of autophagy, as viruses generate membranes for their cytoplasmic replication organelles (Suhy et al. 2000; Nchoutmboube et al. 2013). Autophagy can also be associated with presentation of viral glycoproteins to class I MHC molecules, facilitating recognition of the infected cell by CD8 cytolytic T cells (Tey and Khanna 2012).

Mono-ubiquitination is often associated with either targeted proteins on the cell surface directed to the cellular endosomal sorting complexes required for transport

(**ESCRT**) pathway or in viral assembly, with viral proteins usurping the ESCRT pathway to deliver viral components to the cell surface for assembly and budding; neurotropic viruses employing the vacuolar protein sorting pathway for assembly include VSV, Rabies, LCMV, Japanese encephalitis virus (JEV), HIV, HSV-1, and Epstein-Barr virus (EBV) (Votteler and Sundquist Wesley 2013; Chen and Lamb 2008).

TRIM79α, an ISG, facilitates the ubiquitin-dependent degradation of TBE's viral polymerase but does not recognize the closely related WNV protein (Taylor et al. 2011). As with so many other essential host antiviral pathways, viruses have devised novel evasion tools. HSV-1 and RNA viruses including VSV induce **Siglec-G**, that recruits SHP2 and the E3 Ub ligase c-Cbl to RIG-I, targeting RIG-I for proteolysis (Chen et al. 2013). This pathway, capable of preventing IFN induction by RIG-I, can in turn be antagonized by IFN, inactivating Siglec-G (Chen et al. 2013).

HSV-1 ICP0 induces depletion of CD83 in dendritic cells, diminishing their effectiveness to present viral proteins to T cells (Heilingloh et al. 2014). ICP0 also targets the **ND10** DNA repair complex proteins hDaxx, Sp100 and PML to degradation via the Ub-ligases RNF8 and RNF168 (Lilley et al. 2011). Varicella zoster virus (VZV) ORF61 antagonizes IFN production by targeting **IRF3** for degradation (Zhu et al. 2011).

HIV-1 has two proteins that target cellular proteins for proteosomal removal: Vpu prevents **CD317/tetherin** from retaining nascent viral particles on the cell surface (Schmidt et al. 2011), and Vif targets **APOBEC3**, the cytidine deaminase (Zhang et al. 2012).

There are two other host cell proteins that are similar to Ub and can cross-regulate: **ISG15** and **SUMO**. ISG15 has been shown to play a central role in host-cell antiviral responses in VSV, LCMV, and HSV-1 infections (Campbell and Lenschow 2013; Lenschow 2010).

SUMO-modified proteins are often found in PML nuclear bodies, where proteins may be sequestered (Lallemand-Breitenbach and de The 2010). IFN regulation of MiRs including the Lin28/Let-7 pathway may enhance SUMO expression and inhibition of HIV-1 and HSV-1 infections (Sahin et al. 2014a). IFN treatment and oxidative stress may lead to changes in Sumoylation of target proteins in the PML bodies (Sahin et al. 2014a, b). SUMO conjugation can also be evaded by encephalomyelocarditis virus, HSV-1, VZV, and EBV (Mattoscio et al. 2013).

Tetherin/BST-2/CD317 is an unusual cell surface glycoprotein with both gpi and transmembrane domains holding the protein around lipid rafts (Billcliff et al. 2013). It is expressed by many cell types including neurons, and is induced by both IFN-α/β and IFN-γ (Sarojini et al. 2011). Tetherin is an ISG contributing to antiviral activity for VSV in neurons (Sarojini et al. 2011).

This protein is able to dimerize and tether, hold virus particles on the surface, preventing budding and release of viruses that exit the cell via lipid rafts (Gustin and Douglas 2013). This antiviral pathway is so important that many viruses have developed evasive pathways (Neil 2013; Sauter 2014). HIV Vpu antagonizes tetherin via Ub-modification and degradation, and protecting cells from antibody-dependent cell mediated cytotoxicity (ADCC) (Arias et al. 2014). Glycoproteins of Filoviruses, HSV-1, Sendai, and SIV also block this pathway (Nikovics et al. 2012; Bampi et al. 2013;

Zenner et al. 2013; Gnirss et al. 2014). SIV nef and HSV-2 Env mediate endocytosis of tetherin and intracellular sequestration (Serra-Moreno and Evans 2012). HHV-8 K5 ubiquitinates tetherin (Mansouri et al. 2009). CD317/tetherin is an important host cell glycoprotein found at lipid rafts, whose expression is enhanced by IFNs, and can retain budding viruses.

Reactive Nitrogen and Oxygen Species

The production of superoxide (O_2*), nitric oxide (NO), and peroxynitrite ($ONOO^-$) contribute to elimination of many intracellular pathogens. There are three isoforms of the enzyme responsible for generating NO, nitric oxide synthase (NOS) (Bruckdorfer 2005). In the CNS, NOS-1 is constitutively found in neurons, NOS-2 induced microglia and inflammatory macrophages, and NOS-3 constitutively in astrocytes, ependymal and endothelial cells (Reiss and Komatsu 1998). NO is not only involved in long-term potentiation in the CNS, it also contributes to regulation of blood flow (Murad 2006). Astrocytes and endothelial cells release NO, resulting in dilation of capillaries and increased local perfusion (Moore 2000).

NO has been associated with some inflammatory neurological disorder (Siciliano et al. 2011; Banach et al. 2011; Bernstein et al. 2011). The mechanism of NO-mediated inhibition is covalent modification of viral proteins at cysteine, serine, and tyrosine, resulting in inappropriate folding, assembly, and/or enzyme activity. NO-mediated inhibition and/or pathology in the CNS contributes to the host response for Reovirus, TMEV, HIV-1, SIV, Adenovirus, Junin, Bornavirus, Venezuelan equine encephalitis (VEE), MAIDS, CMV, Murray Valley encephalitis, MHV, Sindbis, VSV, rabies, JEV, and dengue (Andrews et al. 1999; Brodie et al. 1997; Cheeran et al. 2000; Dietzschold and Morimoto 1997; Gendelman et al. 1994; Gomez et al. 2003; Goody et al. 2005; Hooper et al. 2001; Koeberle et al. 2004; Komatsu et al. 1999a; Liao et al. 2012; de Souza et al. 2013; Koustova et al. 2000; Lane et al. 1999; Lin et al. 1998; Mestre et al. 2005; Minagar et al. 2002; Molina-Holgado et al. 1999; Murphy 2000; Navarra et al. 2004; Schoneboom et al. 1999; Thongtan et al. 2010).

NOS-2 is not constitutively expressed but is rapidly induced when macrophages or microglia are exposed to inflammatory cytokines. Microglia produce reactive oxygen species, as well, contributing to neurotoxicity block (Block et al. 2007). However, unlike most of the IFN-regulated effector molecules described above, NOS-1 mRNA is not induced in neurons by IFNγ and other inflammatory cytokines, although treatment of neurons leads to accumulation of the enzyme and greater activity due to degradation of a protein inhibitor (Chesler et al. 2004a, b; Chesler and Reiss 2002; Komatsu et al. 1996; Yang et al. 2007, 2008). This is one instance where IFN-mediated of antiviral activity is at a post-transcriptional level.

Neuropeptides, Peptide Hormones, and Neurotransmitters

Neurons release a variety of peptides and hormones in order to "talk" to other neurons. Many of these proteins have activities outside the synaptic signaling, and can regulate immune responses. Among these molecules are Substance P, Neuropeptide Y (NPY), vasoactive intestinal peptide (VIP/PACAP), neurokinin1 (NK1), and α-melanocyte stimulating hormone (α-MSH) (Dantzer 2004; Brogden et al. 2005; Metz-Boutigue et al. 2003; Prod'homme et al. 2006). NK1 and NPY are inflammatory and may have Defensin-like activity [Defensins are discussed below]. Others like VIP/PACAP are negative modulators, which act principally on dendritic cell induction of regulatory T cells (Delgado et al. 2006; Gonzalez-Rey et al. 2007). Thus, the impact of many neurotrophins, peptides, and neurotransmitters is by modulation of adaptive immune response, as has been seen with CMV (Li et al. 2013a) and HIV-1 infection (Souza et al. 2014).

Adenosine signaling, through surface A1 and A2A adenosine receptors, has been shown to be neuroprotective (Perigolo-Vicente et al. 2014; Latini et al. 1996). The receptors also regulate pain (Sawynok and Liu 2003). In HIV infection, these receptors have been shown to play an anti-inflammatory role (Gilbert et al. 2007). However, A1 receptors may also contribute to neutrophil infiltration, although this is antagonized by A2 receptors (Cronstein et al. 1992). Expression of A2B receptors is induced by HIF-1-α, a cytokine-inducible transcription factor (Kong et al. 2006). ATP, released by cells, can attract neutrophils to tissues via engagement of A3 and P2Y2 receptors. There is reciprocal modulation of cannabinoid receptor expression by adenosine (Carrier et al. 2006), thus signaling by one neurotransmitter can alter the response of neurons to other neurotransmitters. Cannabidiol was shown to be protective in inflammation during TMEV infection via regulation of A2A receptors (Mecha et al. 2013).

Cannabinoids are both endogenously synthesized (endocannabinoids) lipid neurotransmitters and are also found in some plants (e.g., marijuana) or synthetic pharmaceuticals. Two serpentine 7-transmembrane receptors have been well described: CB_1 expressed by neurons and CB_2 expressed by cells of the reticuloendothelial system including microglia (Ullrich et al. 2007). The functions of these receptors are distinct, although the same signaling pathways are used; the serpentine 7-transmembrane receptor is G-protein coupled. These receptors (a) negatively regulate Ca^{2+} channels inhibiting Ca^{2+} release, (b) activate Raf-1, MEK, and ERK, as well as (c) adenyl cyclase which ultimately activates protein kinase A. The CB_1 receptor is associated with hypothermia, immobility, euphoria, and hyperphagia, while the CB_2 receptor is a negative regulator of monocyte and microglial activation, hence immuno-dampening. Thus selective receptor agonists can target either immune responses or neurons. However, this distinction is potentially murky when you consider the regulation of cell-autonomous innate immune responses to viral infections in neurons.

Cannabinoids have been shown to be neuroprotective in Huntington's disease, Parkinson's disease, and multiple sclerosis (Pryce and Baker 2012; Santos 2012; Sagredo et al. 2012; Di Iorio et al. 2013). Cannabinoids have a beneficial impact on TMEV infections and may regulate CD200-CD200R interactions

(Loria et al. 2008; Mecha et al. 2013; Mestre et al. 2005, 2006, 2009). Cannabinoids may contribute to neurogenesis by antagonizing NO production (Kim et al. 2006b). In ischemia (Belayev et al. 1995) or persistent Bornavirus infections (Solbrig et al. 2013; Hooper et al. 2001) where NOS-2 is overactive, NO is associated with pathology, cannabinoids are beneficial. In contrast, in infections where host inflammation and NO are essential to control CNS disease, cannabinoids promoted pathology (Reiss 2010; Herrera et al. 2008). I speculate that cannabinoids may protect the BBB integrity in those settings.

An indirect anti-inflammatory effect of cannabinoids had been found with activation of the nuclear transcription factor peroxisome proliferation activating receptor (**PPAR**) family, described below. CB_2 receptor activation may lead to release of endogenous opioids, which inhibit inflammatory pain (Ibrahim et al. 2006). Somewhat unexpectedly, the antinociceptive and anti-pyretic effects of acetaminophen (Tylenol™) may be due to binding CB_1 receptors.

Δ^9-Tetrahydrocannabinol treatment decreases host resistance to HSV-2 infection (Cabral et al. 1987), probably by inhibiting host inflammatory immune responses against the virally infected cells. In several models where inflammation contributes to pathology, such as TMEV, the synthetic cannabinoid WIN 55,212-2 ameliorates clinical disease (Croxford and Miller 2003); WIN 55 may also induce PGE_2 production (Mestre et al. 2006). However, cannabinoids may contribute to syncytia formation in HIV-E (Noe et al. 1998), leading to pathology. In VSV infection of neuronal cells, activating the CB_1 receptor leads to ~15-fold enhanced viral replication via inhibition of Ca^{2+}-flux and thus impairing the activity of constitutive NOS-1 (Herrera et al. 2008). Therefore, there is no hard and fast rule about the impact of cannabinoid activity on viral infection [reviewed in (Reiss 2010)]. Caution is urged when considering use of these drugs; the effect(s) may be on reticuloendothelial cells or on neurons.

Lipids in Innate Immunity in the CNS

The first part of this section will be devoted to *eicosanoids*, lipid mediators derived from arachidonic acid, liberated from cell membranes by Phospholipase A_2. These include prostaglandins (PG), leukotrienes (LT), lipoxins, epoxides, resolvins, marensins, and other bi-products. The second part of the section will include exogenous sources of these metabolites and lipid modification of cellular proteins. *Cannabinoids* were just discussed. *PPAR agonists* and *Sex hormones* will be discussed below; HPAI axis and neuroendocrine regulation are included here.

The sphingolipid Sphingosine-1-phosphate (**S1P**) regulates lymphocyte traffic from lymph nodes to circulation; it may be bound to the lipid complex HDL in blood (Wilkerson and Argraves 2014). Lymphocytes may express two different receptors S1PR1 and S1PR2; S1PR5 is found on endothelial cells (van Doorn et al. 2012). This pathway has been therapeutically targeted with the drug Fingolimod, an S1P agonist also called FTY720, to sequester proinflammatory T cells away from sites, such as myelin sheaths in multiple sclerosis (Martin and Sospedra 2014;

Halmer et al. 2014). Females express a higher level of S1PR2 than males (Cruz-Orengo et al. 2014), and this may contribute to sex-bias in some autoimmune diseases and responses to infections. I propose that in proinflammatory viral infections of the CNS, where infiltration of cells from circulation contributes to pathology (example: LCMV, although data were not promising (Carr et al. 2013)), use of the S1P agonist may be indicated.

Prostaglandins (PG): Cyclooxygenase (COX) 1 and 2 are the enzymes responsible for the pathway from arachidonic acid leading to the formation of distinct PGs and thromboxane (Ueno et al. 2005). PGJ_2 will be discussed below as an agonist for the nuclear transcription factor PPAR. The family of receptors for PGs is among the 7-transmembrane serpentine surface molecules. The end products have many biologic effects ranging from platelet aggregation (TXA_2) to inflammation and fever (PGE_2) (Ushikubi et al. 2000), but also a profound consequence is immunoregulation, modulating dendritic cell maturation, differentiation, cytokine secretion, and antigen presentation (Harizi and Gualde 2006). The importance of these molecules in physiological processes and pathology has led to drug discovery efforts (Claria 2003). Nonsteroidal anti-inflammatory drugs that block the production of PGs have been shown to be anti-inflammatory in the CNS and somewhat protective for neurodegeneration and cognitive decline in neuroinflammatory diseases (Auriel et al. 2014) and schitzophrenia (Muller et al. 2013).

In the CNS, PGs compromise host responses to VSV, TMEV, JEE, Bornavirus, HSV-1, HIV, enterovirus 71, and EMCV infections (Mestre et al. 2006; Chen and Reiss 2002a; Chen et al. 2000, 2002; Reynolds and Enquist 2006; Steer and Corbett 2003; Lima et al. 2006; Hooks et al. 2006; Rohrenbeck et al. 1999; Tung et al. 2010; Bertin et al. 2012b). The mechanism of interference involves suppression of NO production by NOS isoforms (Chen et al. 2002). Therefore NSAIDs and COXIBs are beneficial not only to prevent fever, aches, and pains, but also to promote recovery from viral infection (Chen and Reiss 2002a; Steer and Corbett 2003).

Leukotrienes (LT): 5-Lipoxygenase (5-LO) is the enzyme responsible for **LT** formation. In general, there is a dynamic ying-yang relationship between the balance of COX and 5-LO activity, since they both use the same initial substrate, arachidonic acid. There are two groups of LT that contribute to pathophysiology based on the receptors used and whether the LT contain cysteine. The CysLT (LTA_4, LTC_4, LTD_4) are associated with fluid production, fibrosis, and airway inflammation in asthma and other pulmonary diseases, while LTB_4 is a potent chemoattractant of neutrophils (Ogawa and Calhoun 2006). High levels of LT are seen secondary to mast cell infiltration or Th2-biased host responses patients infected with RSV, HIV, and CMV viruses (Fullmer et al. 2005; Flamand et al. 2004; Gosselin et al. 2005). More importantly, in the CNS, rather than contribute to pathology and BBB disruption, LT play a beneficial role in recruiting neutrophils and promoting recovery from VSV encephalitis (Chen et al. 2001). LT inhibit early stage HIV infection of microglia (Bertin et al. 2012a), but contribute to recruitment of CD4+ cells by astrocytes (Bertin et al. 2014). Those individuals who take nonsteroidal anti-inflammatory drugs will produce more LT, while those with asthma being treated with LOX inhibitors will have more PG; these common medications can have profound consequences on acute or latent viral infections.

Omega-3 fatty acids consumed in diets rich in cold-water fish (or by capsules) are also anti-inflammatory. They attenuate cytokine production and COX activity, downregulate adhesion molecules, and promote recovery from spinal cord injury (De Caterina et al. 2004; Morris et al. 2006; Serhan 2005b; King et al. 2006; Su et al. 2014). Dietary ω-3 fatty acids may prevent or delay Amyotrophic Lateral Sclerosis (Fitzgerald et al. 2014a). In infections, the data are mixed with benefit in HIV, RSV, HBV, influenza, and HSV keratitis (Razzini and Baronzio 1993; Wu et al. 2012; Bryan et al. 2005; Tam Vincent et al. 2013; Rajasagi et al. 2013), but more rapid death in lymphoma associated with the Murine leukemia virus RadLV (Potworowski et al. 1992). Thus, when host inflammation is essential for controlling viral infection, the immune dampening of ω-3 fatty acids contributes to disease.

Lipoxins (LX) are anti-inflammatory products of arachidonic acid; 15-epi-LXA$_4$ is produced in the presence of aspirin. They are produced at temporally and spatially distinct sites from the inflammatory LT; LX signal through SOCS2 (Machado et al. 2006; Serhan 2005a). LXA$_4$ and 15-epi-LXA$_4$ were associated with attenuation of neural stem cell proliferation and differentiation, in contrast to the activity of LTB$_4$, which induced proliferation (Wada et al. 2006). The literature is sparse concerning the contribution of LXs in the resolution of inflammation associated with viral infections (Shirey et al. 2014; Russell and Schwarze 2014); however, it is possible that LX are produced in the CNS during viral infections.

11,12-Epoxyeicosatrienoic acid (EET) and hydroxyleicosatetraenoic acid (HETE) are the products of Cytochrome P450 Epoxygenase, and are also anti-inflammatory, probably through activation of the PPAR nuclear transcription factor family (discussed below) (Node et al. 1999). However, HETEs can also be produced in oxidative damage; they were elevated in plasma of Dengue virus infected people (Seet et al. 2009). 15-HETE was anti-apoptotic in EBV-transformed B cells natoni (Belfiore et al. 2007). 15- and 20-HETE regulate cerebral blood flow, enhancing perfusion (Gebremedhin et al. 2000).

Resolvins: Additional anti-inflammatory lipid molecules are Resolvins and Protectins, which are produced late in inflammation and promote resolution, including in HSV infection (Bannenberg et al. 2005; Russell and Schwarze 2014). The mechanism by which resolvins promote resolution of inflammation is via induction of miRNA that downregulate proinflammatory mRNA (Recchiuti and Serhan 2012).

Protein Isoprenylation

Statins (HMG CoA inhibitors) were developed and licensed to block cholesterol biosynthesis; however, data indicate that statins diminish inflammation. **Bisphosphonates** block bone resorption by acting on osteoblasts. **Farnesyl transferase** (motif CAAX, found in some proteins with an unpaired Cys) **inhibitors** were hoped to inhibit cellular Ras family activity and thus be powerful cancer therapeutics. These three classes of drugs block distinct enzymes in the same lipid biosynthetic pathway and therefore contribute to regulation of cell autonomous and systemic innate immunity.

These inhibitors of protein-lipid modification can be anti-inflammatory, in part, because protein isoprenylation contributes to production of monokines like IL-1 (Mandey et al. 2006). TLR4 signaling is impaired by statins (Methe et al. 2005), as is LPS-induced AKT phosphorylation (Patel and Corbett 2004). Cytokine activation of microglia is negatively regulated by RhoA, which prevents NF-k B activation. RhoA negatively regulates COX-2 expression, leading to increased PGs levels when isoprenylation is inhibited (Degraeve et al. 2001). These drugs suppress both chemokine production and chemokine receptor expression (Veillard et al. 2006).

However, bisphosphonate treatment results in sustained activation of Rac, Cdc42, and Rho (Dunford et al. 2006), possibly because isoprenylation of phosphatases (PTPases) including the PRL family (phosphatase found in regenerating liver) regulates the activity of Rac (Fiordalisi et al. 2006). Rho/Rho-kinase activity modifies actin cytoskeletal proteins and results in dynamic cellular shape changes as well as the activation of NOS-3, resulting in the production of NO and thus, endothelial cell relaxation; inhibition of protein isoprenylation inhibits this cytoskeletal plasticity and changes in blood-flow dynamics (Rikitake and Liao 2005). These drugs may diminish inflammation by inhibiting diapadesis of inflammatory cells (Walters et al. 2002). Statin treatment is beneficial therapy in multiple sclerosis, not by inducing Th2 or Treg cells, but by inhibiting proliferation of inflammatory T cell (Weber et al. 2014b).

Protein isoprenylation is essential for formation of functional clusters of proteins tethered to cellular membranes (Liao and Laufs 2005). Among the functional complexes which require lipid modification for effective enzymatic activity are the small GTPase activating proteins (GAPs) including RhoGAP (Ligeti and Settleman 2006). Monocyte anti-bacterial activity associated with NADPH oxidase, activated by Rac guanine nuclear exchange factor is negatively regulated by statins (Mizrahi et al. 2005). Ras must be farnesylated to interact with phosphoinoside-3-kinase (Rubio et al. 1999).

With respect to viral infections, there have been several reports that protein isoprenylation is essential to replication of HBV, HCV, HDV, RSV, influenza, and HIV (Acheampong et al. 2007; Einav and Glenn 2003; Mehrbod et al. 2014; Gower and Graham 2001; Huang et al. 2006; Kapadia and Chisari 2005). VSV replication in neurons is inhibited ~15-fold by one of the drugs (D'Agostino, unpublished). In HIV-E, statin treatment was unsuccessful in inhibiting the release of virus to CSF (Probasco et al. 2008), and there was a slight increase in the risk of developing herpes zoster (Antoniou et al. 2014).

Bisphosphonates treatment was beneficial in RSV infections, but contributed to human metapneumovirus pathogenesis (Kolli et al. 2014). They were beneficial in HIV infection by blocking the retroviral integrase (Agapkina et al. 2014). Neuropathology associated with TMEV infection was controlled by bisphosphonates and by SHP-1, a protein tyrosine phosphatase (Christophi and Massa 2009).

Membrane fusion, which is important to initiate many virus infections or to release enveloped virus progeny, is inhibited by isoprenylated SNAREs (Grote et al. 2000). Isoprenylated proteins are not incorporated into lipid rafts (Melkonian et al. 1999). An IFN-inducible antiviral protein, human Guanylate-binding pro-

tein-1 (hGBP-1), a GTPase, is isoprenylated, and Golgi-associated, thus its activity is impaired in the presence of pathway inhibitors (Modiano et al. 2005). Dengue virus assembly was inhibited by statins (Martinez-Gutierrez et al. 2011). Thus, statins, bisphosphonates, or isoprenyl transferase inhibitors may inhibit viral replication, but may also suppress the host IFN-dependent antiviral pathway(s) and inflammation. Overall, inhibition of protein isoprenylation is beneficial to hosts in a wide range of viral infections.

Vitamin D

Plasma levels of Vitamin D and its biological activity are regulated by many factors including diet, sun exposure, and polymorphisms that regulate its receptor and plasma binding protein. In addition to regulating cytokine expression, Vitamin D positively regulates human antimicrobial peptides including Defensins (Wang 2014). Low levels of Vitamin D have been associated with inflammatory diseases including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, atherosclerosis, and asthma (Wobke et al. 2014). Low Vitamin D levels are also associated with increased susceptibility to infections including bacterial, parasitic and HCV, HIV, and influenza (Havers et al. 2014; Kitson et al. 2014; Bryson et al. 2014; Lang et al. 2013).

In the CNS, low Vitamin D levels are a risk factor for multiple sclerosis (Disanto et al. 2012), and normal levels were observed to be neuroprotective and beneficial for maintaining cognition (Anastasiou et al. 2014). Experimental sunlight or ultraviolet light exposure inhibited spinal cord inflammation and reduced demyelination (Wang et al. 2015). In ALS, Vitamin D supplementation may be therapeutic (Gianforcaro and Hamadeh 2014). Serum levels of Epstein-Barr virus were negatively correlated with levels of Vitamin D (Lucas et al. 2011); EBV infection is associated with susceptibility to MS in some individuals (Cocuzza et al. 2014). The mechanism of neuroprotection may be impairment of CD4 extravasation across the BBB (Grishkan et al. 2013). Vitamin D levels have not been studied in other neurotropic viral infections, but we may speculate that normal concentrations may be protective.

Protein Players in Innate Immunity

Many different classes of proteins are critically involved in innate immunity in the CNS. This section will briefly describe the roles of Defensins, Lactoferrin, Complement cascade components, Cytokines and Chemokines. IFNs were discussed earlier.

Defensins

Defensins are small, conserved antimicrobial peptides, produced by many cell types including epithelial and leukocytes, which are found in both very primitive species which lack adaptive immunity and mammals. While inflammatory infiltrating cells may also contribute, in the CNS parenchyma, defensins are synthesized by astrocytes, the choroid plexus, and the hypothalamus (Evans and Harmon 1995; Angeli et al. 1994; Williams et al. 2012, 2014b). Peripherally synthesized defensin molecules can cross the BBB (Schluesener and Meyermann 1995). They have been shown to contribute to elimination of both bacteria and to virus infections by many mechanisms (Wiens et al. 2014; Wilson et al. 2013). In viral infections of the CNS, these include HIV, VZV, HSV, Dengue, adenovirus, and JC (Klotman and Chang 2006; Crack et al. 2012; Rothan et al. 2012; Gwyer Findlay et al. 2013; Wang 2013; Zins et al. 2014). The release of defensins may be regulated by LTB_4 (Flamand et al. 2004).

Lactoferrin is a small secreted, iron-complexed protein that has both antibacterial and antiviral activity. Lactoferrin is found in milk and plasma and secreted by neutrophils (Baynes and Bezwoda 1994). Recent studies suggest that it may contribute to inhibition of innate immune responses during CNS infections with picornaviruses, alphaviruses, papovaviruses, EBV, and HSV (Seganti et al. 2001; Waarts et al. 2005; McCann et al. 2003; Drobni et al. 2004; Valimaa et al. 2009; Zheng et al. 2012).

Complement cascade components and their receptors are expressed both constitutively and can be induced during immune responses in the CNS. Of course, in the classical cascade, specific antibody must first be synthesized and engage its epitopes, inducing conformational changes in IgG which result in exposure of the cryptic C1q binding site and the initiation of the cascade. The alternative and lectin pathways can also induce activation of complement. IgG can cross the BBB, and can, under circumstances of persisting immune responses, be synthesized in the CNS in tertiary lymph nodes (Phares et al. 2013). But that reflects adaptive and not innate immune responses.

The small anaphylatoxins, C3a, C4a, and C5a, which are proteolytic products of the zymogens, are potently active as activators of vascular permeability and chemoattractants for neutrophils. These molecules are produced in the CNS by astrocytes and microglia (Bruder et al. 2004). C5a is a potent recruiter of polymorphonuclear leukocytes (PMNs). In VSV encephalitis C5a was not required for host responses (Chen and Reiss 2002b), the redundancy of chemokines and LTB_4 were sufficient to promote recovery.

Complement receptors include both serpentine 7-transmembrane molecules (which bind C3a, C4a, and C5a) G-protein coupled transmembrane glycoproteins. Endothelial cells and neurons express some complement receptors, including CD46, a measles virus, and Human herpes virus-6 (HHV-6) receptor (Santoro et al. 2003; Schneider-Schaulies et al. 2001; Shusta et al. 2002). Rabies virus infection of the CNS induces the expression of complement genes (Zhao et al. 2011). Complement activation has also been shown to be critical for the development of the adaptive Ab

response for WNV (Mehlhop et al. 2005; Dietzschold et al. 1995). In the presence of antibody, exacerbated C3-dependent pathology was observed in MHV-A59, TMEV, and Coxsackie B3 infections (Burrer et al. 2007).

The complement lectin pathway contributes to protection from West Nile virus infection (Fuchs et al. 2011). Complement contributes to the neurovirulence of Sindbis, HIV, SIV, and Bornavirus infections (Bruder et al. 2004; Speth et al. 2004; Griffin et al. 1997; Dietzschold et al. 1995; Johnston et al. 2001; Phares et al. 2013). In TMEV infection, complement activation contributes to seizures (Libbey et al. 2010). HSV, vaccinia, and the murine gamma herpes virus MHV-68, have developed evasive proteins that prevent complement activity and contribute to their disease pathogenesis (Kapadia et al. 2002).

A vaccinia virus protein has been isolated and has been proposed as a therapeutic when host complement activation is pathogenic in the CNS (Pillay et al. 2005). Recombinant HSV-1 deficient in the complement-interacting $\gamma134.5$ gene product has been proposed as an effective vector for viral oncolysis (Broberg and Hukkanen 2005). Similarly, herbal proteins are also able to block complement and have been suggested as potential neuroprotective therapeutics (Kulkarni et al. 2005). In experimental infection with enterovirus 71 (EV71), a fusion protein of complement receptor 2 (CR2) and the inhibitor Crry prevented complement activation, alleviating local inflammation, and preventing severe disease associated with the picornavirus (Qiu et al. 2012).

Chemokines: IFNs induce expression of chemokines including IFN-inducible 10KD protein (IP-10; CXCL-10; which also has anti-angiogenic activity), Mig/Crg-2 (CXCL-9), and I-TAC (CXCL11). These proteins may also have defensin-like activity, nonspecifically arming anti-microbial responses (Cole et al. 2001). These chemokines recruit neutrophils, natural killer (NK) cells, monocytes, and T cells to the brain (Williams et al. 2014b). They have been shown to be important in the host's response to LCMV, MHV, VSV, and TMEV infections (Rubio et al. 2006; Asensio et al. 1999; Ireland and Reiss 2006; Liu et al. 2000; Palma and Kim 2001). Fractalkine (C3XCL1) has been associated with recruitment of microglia, brain macrophages, and peripheral cells in HIV dementia (Cotter et al. 2002). Chemokine receptors CCR2 and CXCR3 are essential for recruitment of peripheral cells during SFV and WNV encephalitis (Michlmayr et al. 2014).

Many molecules have chemoattractant activity, but are not in the peptide families of chemokines. These include the cytokine IL-12, produced by antigen presenting cells, that can recruit NK cells (Michel et al. 2012), the bacterial tri-peptide f-MetLeuPhe, and the leukotriene LTB_4 for neutrophil recruitment (Lefebvre et al. 2011).

Cytokines are comprised of dozens of different protein mediators, which are generally secreted by one cell and act on the secreting cell (autocrine), locally (paracrine), or systemically (endocrine) to either activate and differentiate another cell type, *or* regulate the activity of another cell. Generally, the receptors are heterodimers of surface glycoproteins, signaling through tyrosine kinase cascades. Although many investigators have tested the effects of individual molecules in experimental systems, in real life, cytokines are secreted as a part of a coordinated program with many different molecules (including receptor antagonists) released at the same time; it is the composite of these mediators' signal transduction pathways that lead

to the outcome. The differentiation state of the downstream cell, the quantity, and duration of exposure determine the response. Cytokines can downregulate their receptors by internalization, leading to desensitization, or induce enhanced expression of their own (and other) receptor and second messengers, which can positively regulate subsequent responses.

In the brain these molecules can be produced by both parenchymal cells and infiltrating inflammatory cells. Two excellent reviews of cytokines and the CNS are a book edited by Ransohoff and Benviste and an article by Campbell (Ransohoff and Benveniste 2005; Campbell 2005). It is the balance between proinflammatory cytokines such as TNF-α, IL-17, or IL-23 and the anti-inflammatory molecules such as IL-4, TGF-β, or IL-10 that ultimately determine the outcome.

Systemically produced cytokines can lead to CNS consequences ranging from the fever response to IL-1 (inducing the production of PGE_2) or TNF-α secretion, resulting in transient disruption of the BBB. Excessive peripheral release of cytokines has been associated with "sickness behavior" (Dantzer 2005; Watkins and Maier 2000).

In infections, proinflammatory cytokines can lead to beneficial outcomes, such as IL-12, TNF-α, or IFN-γ induction of NO which leads to elimination of VSV infections (Komatsu et al. 1996, 1997, 1999a; Ireland and Reiss 2004; Ireland et al. 1999, 2005); however, IL-12/IL-23 and IL-18 are not necessarily critical even if synthesized or administered (Hodges et al. 2001; Ireland et al. 2005). These are important in Sindbis, TMEV, and MHV infections (So et al. 2006; Binder and Griffin 2003; Lane et al. 1996; Olson and Miller 2009; Rempel et al. 2004). Excessive expression of proinflammatory cytokines, in other circumstances, may contribute to pathology (neurovirulence or neurodegeneration) in Bornavirus, JEV, HTLV-1, HIV/SIV, MHV, TMEV, enterovirus 71, LCMV, canine distemper, rabies, and VEE. The proinflammatory cytokine IL-27 induced IL-10 production in MHV-A59 infection, leading to increased demyelination and reduced control of viral replication (de Aquino et al. 2014). Ironically, the anti-inflammatory cytokine IL-4 may be associated with resistance to human WNV infection in a GWAS study (Qian et al. 2014). Cytokines are essential mediators in viral infections of the CNS. Some cytokines are neuropoietic, promoting recovery (Bauer et al. 2007). The timing, quantity, and balance of these bioactive molecules determine the outcome: recovery or pathology.

Transcription Factors Regulating Inflammation

Many transcription factor families regulate responses, and the roles of IFN-inducible STATs have been discussed above. In this section, three classes of transcriptional factors will be described: Hypoxia-inducible factor, Peroxisome proliferation activating receptor, and High mobility group-1 protein. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor whose expression is triggered by transient hypoxia (or ischemia/stroke); it induces the expression of a number of genes including defensins, the adenosine A_2B receptor, Vascular Endothelial Growth Factor (VEGF), COX-2, NOS-2, and NOS-3 (Kong et al. 2006; Hellwig-Burgel et al. 2005; Peyssonaux and Johnson 2004). VEGF regulates not only BBB permeability, but also angiogenesis. HIF-1α

expression can be induced by IL-1, TNF-α, and possibly TLR agonists (Hellwig-Burgel et al. 2005; Argaw et al. 2006). It is expressed during inflammatory and demyelinating diseases (Aboul-Enein et al. 2003). In studies with viral vectors for oncolysis in the CNS, HIF-1α expression was enhanced (Shen et al. 2006; Post et al. 2004). Thus, HIF-1α expression, whether elicited by transient vascular compromise or cytokine expression, enhances the innate antiviral (and anti-bacterial) gene expression and may lead to increased BBB perfusion of the local area.

Peroxisome Proliferating Activating Receptors, nuclear hormone transcription factors, have three isoforms α, β, and γ, each with distinct activity and expression. PPAR-γ, the canonical nuclear hormone receptor involved in muscle glucose uptake and lipid homeostasis and cell differentiation, is translated as two splice variants, γ1 and γ2. PPAR-γ2, 30 amino acids longer than γ1, is expressed in high levels of adipose tissue. PPAR-γ ligands are polyunsaturated fatty acids, eicosanoids, FA oxidation products (13-HODE and 15-HETE), J-series prostaglandins (15-deoxy-D12,14-prostaglandin J$_2$), some nonsteroidal anti-inflammatory drugs (NSAIDS), and insulin sensitizing thiazolidinediones (TZDs). PPAR-γ functions as an obligate heterodimer with Retinoic X receptor (RXR) to activate transcription by binding to 5′ promoters of target genes (Grygiel-Gorniak 2014; Fidaleo et al. 2014).

PPAR-γ agonists modulate inflammatory responses in the CNS, resulting in the reduction of iNOS in cerebellar granule cells. PPAR-γ signaling has anti-inflammatory function in EAE, PPAR-γ agonists alleviate symptoms with antagonists performing the opposite, indicating regulation of auto-reactive Th1 and Th17 cells (Kanakasabai et al. 2010). PPAR-γ also can regulate pathologic immune responses within the CNS in MS (Shukla et al. 2010). Alzheimer's disease is a severe neurodegenerative disease characterized by the accumulation of amyloid plaques accompanied with activated microglia. TZD treatment in in vitro experiments with microglia and monocytes attenuated the secretion of proinflammatory cytokines. Medium from TZD-treated microglia was neuroprotective (Drew et al. 2006).

Infection by Adenovirus 36 induces PPAR expression, and increases insulin sensitivity (Pasarica et al. 2006). In vitro treatment of cells with PPAR agonists inhibited replication of RSV, HHV8, HCV, HIV, and VSV (Rakic et al. 2006; Bryan et al. 2005; Arnold and Konig 2006; Herrera et al. 2008), although the mechanism(s) by which this inhibition occurred have not been elucidated. However, HBV X-associated protein 2 complexes with PPAR and inactivates it (Sumanasekera et al. 2003), an evasive pathway. Thus treatment with PPAR agonists, such as TZDs, may be beneficial for treatment of viral encephalitis both as potential antiviral compounds, and as anti-inflammatory drugs in infections where pathology is associated with inflammation, such as Bornaviral disease and HIV infection (Kim et al. 2012).

High Mobility Group protein B1 (HMGB1) is unique among transcription factors as it is found not only in the nucleus, but also in the cytoplasm associated with α-Synuclein filaments (Lindersson et al. 2004) and is actively released as an alarmin. Its expression may be upregulated by IFN (Seeler et al. 2001). HMGB1 may engage AMIGO receptors of neurons where it regulates neurite outgrowth, TLR 2 and TLR 4, or the Receptor for Advanced Glycation Endproducts (RAGE) which results in a proinflammatory response by microglia, macrophages, and dendritic cell maturation (O'Connor et al. 2003).

HMGB1 release has been shown to be neurotoxic in ischemia, Alzheimer's disease (Kim et al. 2006a) and in Bornavirus disease, HTLV-1, HIV-1, and WNV infections (Troseid et al. 2013; Kimura and Mori 2014; Zhao et al. 2006; Chu and Ng 2003). HMGB1 is a Janus molecule with both regulatory transcriptional activity and signaling of tissue damage; it may be important in eliciting innate immunity during viral encephalitis.

BBB

Within the CNS, there are anatomically distinct regions that have some constitutive vascular permeability (Circumventricular organ, choroid plexus, for example), but most areas are highly restricted in access to circulating cells and proteins. Astrocytes regulate the perfusion of the parenchyma by controlling vasodilation of the cerebrovascular capillaries through the activity of NOS-3 (Sporbert et al. 1999; Komatsu et al. 1999b). The BBB is associated with the immune privilege of the brain and separates the CNS from peripheral circulation and immune surveillance that is characteristic of the periphery. Entry of cells requires adhesion to the brain microvascular endothelium, release of MMPs to degrade tight junctions and the extracellular matrix, as well as migration along a gradient of chemoattracting molecules (Bechmann et al. 2007; Arima et al. 2013). The chemoattracting molecules for circulating cells range from LTB_4 to complement products, chemokines, cytokines, FLT3L, and even ATP (all discussed in the relevant sections, above).

The BBB breakdown associated with infection results from excessive normal physiological process regulating blood flow within the CNS (Proescholdt et al. 1999; Abbott et al. 2006). Activation leads to NOS-3-expressing astrocytes to release NO, which induces guanadyl cyclase to produce cGMP, leading to endothelial and smooth muscle cell relaxation. Other mediators such as the small complement cascade mediators C3a, C4a and C5a, VEGF and PGE_2 can also lead to the relaxation and increased permeability of the BBB.

A hallmark of many viral infections including VSV, Rabies, Flaviviruses, HIV, TMEV, and WNV (Daniels et al. 2014; Wang et al. 2013; Neal 2014; Johnson et al. 2014; Williams et al. 2014a; Chen et al. 2002) is the breakdown of the BBB. However the global breakdown of the BBB seen in fatal LCMV (Kang and McGavern 2010) and in fatal VSV infections is extreme, and unusual. In most cases, the overall integrity of the BBB is maintained, but in discrete regions, there is increased perfusion leading to entry of normally excluded proteins from circulation.

Apoptosis and Autophagy

Cells under stress from viral infection, TNF-family cytokines, CTL recognition, as well as many other stimulate can undergo programmed cell death (apoptosis) (Danial and Korsmeyer 2004). I will not review the cellular pathways which lead to genome

fragmentation and membrane inversion, but will focus, instead, on associations between viral infection and apoptosis. Cells which commit suicide in this manner may spare the host from continued viral replication, a benefit, especially since most cells can be replaced by stem cells in that organ; however, if the infected cell undergoing apoptosis were a neuron, significant consequences might ensue (Perkins 2005).

Neurotropic viruses which elicit apoptosis include alphaviruses (Griffin 2005), Flaviviruses (Clarke et al. 2014), Picornaviruses (Ruller et al. 2012), VSV (Gaddy and Lyles 2007), Rabies (Fu and Jackson 2005), coronaviruses (Desforges et al. 2014), LCMV (Sun et al. 2014), reovirus (Dionne et al. 2013), JC (Merabova et al. 2012), HIV-1 (Geffin and McCarthy 2013), and HTLV-1 (Marriott and Semmes 2005). In fact, apoptosis is such an important cellular defensive response to viral infections that poxviruses have developed an evasive pathway, using serine protease inhibitors (serpins) (Taylor and Barry 2006). But, scientists are clever and have selected apoptosis as a tool for viral oncolysis.

At other times, viral infections or cellular stress from starvation can lead to recycling of large volumes of cytoplasmic contents by generation of vesicles which fuse with lysosomes (**autophagy**, self-eating) (Deretic 2005). This pathway can become dysregulated, resulting in inflammation and neurodegenerative diseases (Deretic et al. 2013; Noch and Khalili 2013; He and Klionsky 2006).

Some picornaviruses use this cellular response to develop additional membranes on which to replicate (Jackson et al. 2005). In the CNS infections caused by Coxsackie B3 (Tabor-Godwin et al. 2012), Sindbis (Sumpter and Levine 2011), HIV (Levine and Sodora 2006), LCMV (El-Azami-El-Idrissi et al. 2005), and HSV (Korom et al. 2013) autophagy-associated pathology has been reported. Thus, in general, autophagy is an innate host cellular response to suppress viral infection, however, some viruses, to their benefit, can manipulate it.

Parenchymal and Inflammatory Cells in Innate Immunity in the CNS

Infiltration of Peripheral Circulating Cells

Normally there are very few lymphocytes, neutrophils, and NK cells in brain parenchyma. Infiltration of inflammatory cells ranging from PMNs to NK cells to macrophages and finally lymphocytes takes place in response to a series of signals from both chemoattractant molecules and orchestrated binding to microvascular endothelial cell surface molecules (Williams et al. 2001; Luster et al. 2005). For cells to cross the endothelial vessel wall, they must diapedese and then digest the basement membrane with MMPs. This review will not discuss the infiltration of antigen-specific T cells or B cells, as it is limited to innate immune responses.

Neutrophils are the first cell to infiltrate sites of viral infection. Chemoattractants for neutrophils include Adenosine, ATP, f-MetLeuPhe, C5a, LTB$_4$, and chemokines (Gabriel et al. 2013). As described above, they produce defensins, cytokines, media-

tors from aracodonic acid, and other bioactive compounds. In VSV encephalitis, LTB_4 and chemokines, but not C5a, are essential (Ireland and Reiss 2006; Chen and Reiss 2002b; Chen et al. 2001). PMN infiltration is also characteristic of Murray Valley encephalitis, MHV, HSV-1, TMEV, Western equine encephalitis, and adenovirus infections (Libbey et al. 2011; Weiss et al. 2007; Matthews et al. 2000; Reed et al. 2005; Wakimoto et al. 2003; Welsh et al. 2004; Weinberg et al. 2007; Zhou et al. 2003; Campbell et al. 2001; Bell et al. 1996).

NK cells are generally the second cell type to diapedese in response to viral infections of the CNS in response to both chemokines and IL-12. NK cells nonspecifically recognize patterns of receptor expression on cells and are sensitive to low levels of MHC molecules, and, when activated, release IFN-γ, perforin and granzymes, like CD8+ CTL. NK cells have been associated with the host response to JEV, WNV, Sindbis, MHV, Bornavirus, EBV, HSV-1, VSV, SIV, CMV, TMEV, and enterovirus 71 (Hatalski et al. 1998; Christian et al. 1996; Wensman et al. 2011; Fernandes et al. 2011; Wang et al. 2013; Mott et al. 2011; Brehin et al. 2008; Larena et al. 2013; Ogura et al. 2013). NK cells contribute not only lytic activity against virally infected cells, but also are a significant source of IFN-γ secretion, both of which may regulate viral replication.

Antigen Processing and Presentation

Pioneering work by the late Helen Cserr and her colleagues including Paul Knopf explored lymphatic drainage of soluble antigens and their ability to evoke an acquired immune response (Knopf et al. 1995). This drainage is polarized from rostral to caudal, and is modest and does not include the hallmarks of peripheral tissue dendritic cells bearing antigens to the draining lymph nodes.

Antigen processing and presentation is at the interface between the innate and adaptive immune responses to pathogens. There is little constitutive expression of Class II MHC molecules in the undisturbed CNS; however, both **astrocytes and microglia** readily express these molecules in response to inflammatory cytokines, especially IFN-γ (Gresser et al. 2000). Infection indirectly induces the expression of MHC II and enhances the expression of MHC I by parenchymal cells (Berman et al. 1998; Abraham and Manjunath 2006; Aguirre and Miller 2002; Alldinger et al. 1996; Caplazi and Ehrensperger 1998).

Perivascular macrophages have been shown to be an important player in antigen presentation for the brain in infections and autoimmune disease (Williams and Hickey 2002). Macrophages and **microglia** may produce proinflammatory (M1) or anti-inflammatory (M2) cytokines and bioactive mediators; M2 microglia antagonize neuroinflammation (Cherry et al. 2014). Mi cells contain multimolecular complexes called inflammasomes, intracellular sensors for pathogens and danger signals; these inflammasomes generate substantial quantities of proinflammatory IL-1 and IL-18 (Walsh et al. 2014). M1 microglia are characteristic of VSV, neurotropic influenza virus, and TMEV infections (Jurgens et al. 2012; Son et al. 2009; Steel et al. 2014).

Mast cells are often overlooked except in studies of Type 1 hypesensitivities. Mast cells can participate with glia in neuroinflammation (Skaper et al. 2014). IL-33, produced by glia, would promote mast cells; in TMEV infections, IL-33 was produced (Hudson et al. 2008). In HIV-E with immune reconstitution syndrome after antiretroviral therapy, mast cells contribute to CNS pathology (Rushing et al. 2008).

Dendritic cells are the principal antigen presenting cells in the periphery and are a complex group of cells whose phenotypes rival T cell subsets (Guilliams et al. 2014; Cohn and Delamarre 2014). They are extremely difficult to detect in undisturbed brain tissue. During immune responses in the CNS, it is possible to find cells expressing dendritic cell markers (Matyszak and Perry 1997; Ambrosini et al. 2005). In addition to any chemokines, Flt3L has been shown to recruit dendritic cells to the CNS (Curtin et al. 2006). Parenchymal dendritic cells have numerous phenotypes (D'Agostino et al. 2012a), and VSV infection induces CD103$^+$ CD11b$^+$ cells (D'Agostino et al. 2012b). Dendritic cell responses are age dependent and may contribute to the susceptibility of immature hosts to some forms of viral encephalitis (Taylor et al. 2014). However, the microenvironment during which dendritic cells are exposed to virus can determine whether pro-inflammatory or Treg responses are found (Durrant et al. 2013; Martinez et al. 2014).

HPAI Axis and Neural-Endocrine Regulation

The hypothalamic-pituitary-adrenal-immune (HPAI) *axis* controls not only fight-or-flight in response to stressors, but also critical control of immune responses to infections. There are short-term and chronic stress manifestations of this (Eskandari and Sternberg 2002; Shanks et al. 1998), with long-term compromise of immune responses to viral infections (Silverman et al. 2005). This may be manifest as alterations in the humoral response to viral infection (Ijaz et al. 1990). Acute stress may also alter the integrity of the BBB (Esposito et al. 2001), thus potentially permitting entry to otherwise excluded viruses.

Sympathetic Nervous System

Chemical sympathectomy, achieved by infusion of 6-hydroxydopamine, has profound effects on the peripheral immune response, as there is sympathetic innervation of the spleen and lymph nodes (Callahan et al. 1998). Hosts are more susceptible to bacterial, VZV reactivation, and HSV-1 infections (Cao et al. 2002; Massad et al. 2004; Leo et al. 1998; Templeton et al. 2008), but when hosts are already immune suppressed, whether by malnutrition or by lentivirus infections, they are not further compromised (Kelley et al. 2002; Gonzalez-Ariki and Husband 1999). We tested whether chemical sympathectomy altered the ability of peripheral plasmacytoid dendritic cells to produce IFN-β in response to VSV infection of the CNS, and

found no contribution of innervation of secondary lymphoid organs in this response (Trottier et al. 2007). However, production of proinflammatory cytokines and increased pathology were observed in influenza virus infection to be associated with the sympathetic response (Grebe et al. 2010).

Cholinergic pathways have been shown to be anti-inflammatory in bacterial model systems and ischemia-reperfusion injury (Tracey 2007), inhibiting cytokine production and tissue injury in models such as colitis (Sun et al. 2013). In a transgenic model, HIV-1 was associated with learning deficits; activation of the cholinergic pathway with nicotine did not ameliorate the loss vigorito (Vigorito et al. 2013). But, there are no published reports in the literature on the impact of this regulatory neurotransmitter pathway on neurotropic viral infections.

Leptin was originally identified as the gene product deficient in obese mice and was found to regulate energy balance, but like so many other effector molecules, has many other activities. Proinflammatory cytokines, induced during infections, can upregulate production of leptin (Yu et al. 2014), and lead to anorexia (Langhans 2000). Central leptin and insulin resistance has been associated with Adenovirus (SMAM-1 and Ad36) infection, leading to obesity (Wierucka-Rybak and Bojanowska 2014). Recent evidence suggests that this adipocyte-produced protein is also immunoregulatory and is, in fact, a proinflammatory cytokine (Lord 2006). Leptin is pathogenic in EAE (Matarese et al. 2002) by virtue of its action on dendritic cells, resulting in the induction of Th1 responses (Mattioli et al. 2005) and its inhibition of thymic apoptosis (Mansour et al. 2006). In experimentally induced obese mice, more severe influenza pathology was associated with leptin (Zhang et al. 2013a). Well-nourished infants, with elevated leptin levels, were more susceptible to Dengue hemorrhagic fever, than were thinner children (Libraty et al. 2014). High leptin levels were observed in HCV-infected people with chronic fatigue symptoms (El-Gindy et al. 2012). In contrast, low levels of leptin are observed in HIV infections, and exaggerated in those patients with lipodystrophy veloso (Veloso et al. 2012). Therefore, leptin may be a potential target for therapeutic intervention in persistent inflammatory infections of the CNS such as HIV-E and Bornaviral disease.

Sex hormones regulate more pathways than just those in secondary sexual organs.

Estrogen is neuroprotective in infection, Alzheimer's disease, traumatic injury, and ischemia (Barreto et al. 2014; Cue et al. 2015). Estrogen has profound immuno-modulating effects ranging from induction of NOS-3, and thus increased vascular perfusion (Hayashi et al. 1997). Selective estrogen receptor modulators enhance neurogenesis and spine density (Khan et al. 2015). Movement disorders including Parkinson's disease are more frequent in males (Lubomski et al. 2014). Estrogen positively regulates expression of IFN-γ (Fox et al. 1991); this is clearly linked with the increased frequency of females who have Th1-associated autoimmune diseases such as EAE/MS (Whitacre et al. 1999).

Additionally, sex hormones regulate PPARs, and can influence the severity of EAE (Dunn et al. 2007). Females may be more resistant to some viral infections due to enhanced Th1 responses, including VSV, TMEV, and HSV-1 (Markle and Fish 2014; Forger et al. 1991; Fuller et al. 2005; Peter and Sevall 2001).

Androgens may be immunosuppressive by inhibiting Th1 differentiation (Kissick et al. 2014). This may contribute to diminished efficacy of vaccination and the production of anti-influenza antibody by males (Furman et al. 2014). Hepatitis B and HCV disease is more severe in males, and correlated with testosterone levels (Tian et al. 2012; White et al. 2012).

There is an effect of host sex in viral infections of the CNS. Female mice are more resistant than males to lethal VSV infections (Barna et al. 1996), and show improved clearance of MHV and Semliki Forest virus infection from oligodendrocytes (Fazakerley et al. 2006; Parra et al. 1999). However, female mice undergo more severe demyelination in TMEV infections (Fuller et al. 2005). HIV-E and HIV-dementia incidence may be lower in females due to estrogen effects on immune responses (Wilson et al. 2006). Thus, where inflammation is beneficial to clearing virus and resolving infection, females are at an advantage. In contrast, where inflammation contributes to viral disease pathology in the CNS, females are disproportionately affected.

Summary and Speculation

Innate immunity in the CNS is complex and includes protein effectors (IFNs, cytokines, chemokines, defensins, complement, lactoferrin, and other molecules), lipid mediators (PGs, LTs, Cannabinoids, etc.), small diffusible molecules (NO, ONOO⁻), and both parenchymal and inflammatory cells. These responses are highly regulated and are triggered, in part, by receptors that bind common pathogen-associated or damage-associated molecules. Combined, these responses provide a critical barrier, controlling viral replication until adaptive immune responses are marshalled. Inflammation is essential, but must be carefully controlled to prevent tissue damage and pathology. Virtually every pathway has regulation (e.g., kinases and phosphatases) that ultimately determines the magnitude and then the resolution of responses. We are still learning about the essential pathways and their controls, about how drugs may alter the dynamic equilibrium, and in which situations responses need to be ramped up or downregulated. Nonetheless, innate immune responses are critically essential in the central nervous system, to buy the host time for the adaptive immune response to mature and provide antigen-specific effector T cells and antibody to the viral infection. I predict we will make many future advances that will benefit the health of the populations who are infected with neurotropic viruses.

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