J Neuroimmune Pharmacol (2010) 5:267–270
DOI 10.1007/s11481-010-9231-x

GUEST COMMENTARY

Viral Infections of the Central Nervous System: Pathogenesis to Therapeutics

Samantha S. Soldan · Steven Jacobson

Received: 22 June 2010 / Accepted: 25 June 2010 / Published online: 24 July 2010

Keywords neurovirology · HIV-1 · antivirals · HAART · HTLV-I · HERVs · PML · alphaherpesvirus · TMEV · measles · arbovirus · encephalitides · MHV · multiple sclerosis · coronavirus · neuroinflammation · immunomodulatory

Viral infections of the CNS have been implicated in many debilitating illnesses including chronic neurodegenerative and neuroinflammatory disorders, neuropsychiatric conditions, acute encephalitis, and CNS malignancies. Although the effects of these manifold diseases are devastating, leading to death in some instances, the armamentarium of effective vaccines and therapeutics at our disposal to prevent and treat virus-mediated disorders of the CNS is astoundingly limited. It is, therefore, critical that we achieve a better understanding of the common mechanisms of neuroinflammation and neurodegeneration involved in these disorders so that more effective therapeutics can be developed. In this special issue of the Journal of Neuroimmune Pharmacology, we have assembled an extraordinary collection of contributions, including both comprehensive reviews and primary research articles, from leaders in the field of neurovirology. The manuscripts contained herein focus on a variety of CNS diseases caused by or associated with viruses from disparate families and highlight virus-induced mechanisms of neuropathogenesis supported by both clinical and basic research findings. Ultimately, the elucidation of pathways of virus-mediated neurotoxicity and the neuroinflammatory processes underlying these various conditions will lead to the development of treatment strategies for heterogenous disorders of the CNS associated with viral infection.

The neuropathogenesis of HIV-associated neurocognitive disorders (HAND) is complex, but it is clear that both innate and adaptive immune factors are involved in disease progression. The contribution from Dr. Shah and colleagues provides an excellent review of the role of the adaptive and innate immune systems in HIV pathogenesis. Innate immune factors are important, not only in mediating inflammation, but also in directly inhibiting HIV replication (Shah et al. 2010). In addition, the contributions of inflammatory mediators, cytokines and chemokines in particular, to HIV-1 disease are discussed at length (Shah et al. 2010). Both macrophages and astrocytes contribute to inflammation and neuronal pathology in the CNS of infected individuals and, although much of the damage is mediated by pro-inflammatory cytokines and chemokines, it is now appreciated that chemokines may also have a neuroprotective role and act as neurotransmitters and neuromodulators. Therefore, a better understanding of the contributions of both the innate and adaptive arms of the immune system to chronic virus diseases of the CNS is needed and may ultimately be harnessed for therapeutic gain.

The use of antiretroviral therapy (ART) for HIV-1 infection has improved virological control and increased the life expectancy of HIV-infected individuals. However, despite the availability of these potent antivirals, the prevalence of HAND has increased, underscoring the need

S. S. Soldan (✉)
Department of Neurology, University of Pennsylvania,
Philadelphia, PA 19104-4283, USA
e-mail: sssoldan@mail.med.upenn.edu

S. Jacobson
Viral Immunology Section, Neuroimmunology Branch, NIH,
Building 10, Room 5C-103,
Bethesda, MD 20892, USA
e-mail: jacobsons@ninds.nih.gov

for neuroprotective therapies to be used in combination with ART. Accordingly, the objectives of the next generation of therapeutics for HIV infection include countering molecular and immune-mediated mechanisms of neurodegeneration (Lindl et al. 2010; Shah et al. 2010). In this special issue, Lindl et al. provide a comprehensive overview of the neuropathogenesis of HAND with a focus on the role of inflammation, excitotoxicity, and oxidative stress (Lindl et al. 2010). Candidate therapeutics targeting inflammation (Minocycline), excitotoxicity (Memantine), and oxidative stress (Selegiline) are discussed for their potential as neuroprotective agents and adjunctive therapies to current ART for patients with or at high risk for HAND. In their original research article, Gorantla and colleagues suggest that cannabinoid receptor type 2 (CB2R) agonists also have potential as an adjunctive therapy for HAND (Gorantla et al. 2010). Here, the murine human peripheral blood lympohocyte/HIV-1 encephalitis model (hu-PBL/HIVE) is used to examine CB2R expression and the ability of Gp1a, a highly selective CB2R agonist, to modulate disease (Gorantla et al. 2010). Increased CB2R expression and microglial activation was demonstrated in the brains of Hu-PBL/HIVE mice. Daily Gp1a treatment reduced infiltration of human cells to the mouse brain, reduced markers of activation, and down-modulated CCR5 expression on human cells in the spleen (Gorantla et al. 2010).

Other retroviruses, including HTLV-I and human endogenous retroviruses (HERVs) have been implicated in neurologic disease. The human retrovirus human T-lymphotropic virus type I (HTLV-1) causes HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in a small percentage (<5%) of infected individuals. Matsuura and colleagues provide a current perspective on host–virus interactions in HTLV-I infection and highlight the role of high proviral loads and a robust CD8+ T cell response in the development of HAM/TSP (Matsuura et al. 2010). As in HAND, the production of cytokines/chemokines may adversely affect resident cells in the CNS, contributing to the neurodegeneration manifested in HAM/TSP (Matsuura et al. 2010). Of interest, recent reports from Dr. Jacobson's group have demonstrated that CD244 (a signaling lymphocyte activation molecule (SLAM) family receptor) and SLAM-associated protein (SAP) are significantly higher in HAM/TSP compared to asymptomatic carriers and uninfected individuals (reviewed in Matsuura et al. (2010)) suggesting that differential expression of SAP in CD8+ T cells may result in more extensive degranulation and contribute to the high cytotoxic T lymphocyte (CTL) response observed in patients with HAM/TSP. Recent reports, endogenous retroviruses may also play a role in several disorders of the CNS. In this special issue, the evidence for a controversial association of HERV-H/F and HERV-W/MSRV with multiple sclerosis and HERV-K and HERV-W with schizophrenia and bipolar disorder are presented (Christensen 2010). In addition, Christensen makes an interesting case for the potential role of HERVS as co-factors in retrovirus-mediated neurological disorders including HAD and HAM/TSP and argues that HERVs may present a link between genetic predisposition and environmental factors in a variety of human diseases (Christensen 2010).

Multiple sclerosis (MS) is the most common neuroinflammatory disorder of the CNS and there are many similarities between the inflammatory cascades involved in the pathogenesis of MS and those observed in both HAND and HAM/TSP. Infectious agents have been implicated in the pathogenesis of MS for over 100 years, but no single causative agent has been definitively identified. We have included several contributions that support the role of viruses in the complex etiology of MS. Currently, two herpes viruses, Epstein–Barr virus (EBV) and human herpesvirus-6 (HHV-6), are under active investigation as candidate pathogens in MS. Dr. Ascheiro and Dr. Munger have contributed a compelling review that highlights the epidemiological evidence for the role of Epstein–Barr virus in MS (Ascherio and Munger 2010). Possible mechanisms to explain the relationship between EBV and MS include bystander damage by EBV-specific CTLs targeting EBV-infected B cells that infiltrate the MS brain (Ascherio and Munger 2010). In addition, Yao et al. have suggested that the binding of HHV-6 to its receptor, CD46, triggers a pro-inflammatory response that could contribute to the CNS tissue damage observed in MS (Yao et al. 2010). In this report, Yao et al. demonstrate that CD3/CD46 crosslinking induces expression of IL-1β and IL-17A in T cells from MS patients, suggesting a potential mechanism of virus-induced neuroinflammation in this disorder (Yao et al. 2010).

Infectious animal models in which viruses cause demyelinating disease, often after long incubation periods and a relapsing remitting disease course, support the role for viruses in the pathogenesis of MS. In this special issue Theiler's murine encephalomyelitis virus (TMEV) and mouse hepatitis virus (MHV) are highlighted as infectious murine models for MS. Neurotropic strains of murine coronavirus (mouse hepatitis virus, MHV) cause acute encephalitis followed by chronic demyelination in survivors, making MHV an appropriate infectious animal model for MS. In their discussion of the pathogenesis of murine coronavirus in the CNS, virus gene determinants of pathogenesis, receptor usage, cellular tropism, and the immune components involved in control of infection, clearance, and inhibition of reactivation of MHV are discussed (Bender and Weiss 2010). This review is an excellent resource for understanding the complex interplay between virus and host factors in virus-mediated disorders

of the CNS (Bender and Weiss 2010). In addition, Tsunoda et al. present an overview of the TMEV model for MS and highlight important similarities and differences between TMEV and experimental autoimmune encephalomyelitis (EAE) as models for MS (Tsunoda and Fujinami 2009). Importantly, TMEV infection is useful for studying several aspects of the neuropathogenesis of MS including neuronal apoptosis, axonal damage, humoral responses, the contributions of CD4+ and CD8+ T cells, T cell receptor usage, adhesion molecules, and the direct consequences of virus infection (Tsunoda and Fujinami 2009). The mechanisms by which TMEV penetrates vascular barriers to the CNS are discussed further by Kang and colleagues (Kang and McGavern 2010) who have provided insight into the varied mechanisms by which microbes, both viruses and protozoan parasites, compromise and penetrate vascular barriers to the CNS (Kang and McGavern 2010)

In addition to neurodegenerative and neuroinflammatory disorders of the CNS, viruses have been implicated in a number of CNS malignancies. Polyomaviruses and herpesviruses are frequently detected in many CNS tumors; yet, their causative role in these malignancies is unclear and sometimes controversial. Saddawi-Knefka and Crawford have provided a summary of human studies investigating the role of viruses in primary CNS malignancies for this special issue (Saddawi-Konefka and Crawford 2010). Moreover, potential oncomodulatory mechanisms of viral-associated CNS disease are discussed. Importantly, the authors outline suggestions on how to better establish the role of viruses in CNS malignancies, including widespread cooperative validation of techniques used in virus detection, a focus on a better understanding of virus tropisms in normal brain at different ages, and the design and implementation of new clinical trials using specific antivirals or targeting CNS neuroimmunity to induce a cell-mediated or humoral antiviral response. In addition, this issue includes a timely overview of progressive multifocal leukoencephalopathy (PML) and its causative agent, JC virus (Marshall and Major 2010). The development of PML is associated with suppression or modulation of the immune system. Once chiefly a disease found in AIDS patients and those with hematologic malignancies, PML is a growing concern for patients undergoing immunomodulatory treatment for autoimmune diseases including MS. The authors effectively make the case that the role of the immune system in JC virus dissemination is critical to our understanding of the neuropathogenesis of PML and in the development of therapeutic targets for autoimmune diseases.

The identification of host gene products involved in viral infection is essential to understanding virus pathogenesis and in the development of new treatment modalities. In their contribution to this special issue, Szpara et al. compare results from seven microarray studies focused on the host response of either neural tissue or isolated neurons to alphaherpesvirus (herpes simplex virus type 1 or pseudorabies virus) infection (Szpara et al. 2010). This meta-analysis identified several common host responses in different species to various alphaherpesvirus strains in all phases of infection—highlighting the likely importance of these genes and gene families in virus infection and/or in the host's defense. Genes affected by alphaherpesvirus infection include genes involved in the immune system, signal transduction genes, transcriptional regulators, genes involved in the regulation of host cytoskeletal proteins and molecular motors, proteolytic enzyme genes, potassium-voltage-gated channel protein genes, and most extracellular matrix gene families. Importantly, this analysis includes previously unpublished data, and provides an impressive overview of gene expression affected by alphaherpesvirus infection (Szpara et al. 2010).

This special issue of the Journal of Neuroimmune Pharmacology describes both frequent and infrequent virus-mediated disorders of the CNS. Arboviruses, for example, are distributed worldwide, representing nearly 30% of all emerging infectious diseases in the last decade. Many arboviruses are important human and veterinary pathogens with a propensity for devastating CNS involvement. Here, Hollidge et al. describe the natural history of arboviral infections and focus on mechanisms of neuroinvasion and neurovirulence in arboviruses that are frequent causes of neurologic disease in humans, including members of the genera *Flavivirus* and *Alphavirus* and the family *Bunyaviridae*. Importantly, the pressing need for improved vaccination and therapeutic strategies for these emerging viruses is discussed (Hollidge et al. 2010). While many of the neurological disorders included in this special issue are significant and emerging public health issues, why invest valuable resources in studying the neuropathogenesis of less common neurodegenerative disorders with a viral etiology? In Blue Moon Neurovirology: The Merits of Studying Rare CNS Diseases of Viral Origin, O'Donnell and Rall present a convincing argument for the myriad benefits of studying virus-mediated disorders of the CNS that are relatively uncommon through highlighting the impact of studies of measles virus-induced disorders of the CNS on our understanding of host influences on virus pathogenesis, the role of neurons in the induction of host immunity, and the potential basis of age-dependent pathogenesis. This review gives us an interesting perspective on the insights that studies of rare, virus-induced CNS disorders may provide into multiple neurotropic pathogens and the broader field of viral pathogenesis (O'Donnell and Rall 2010).

This has been an exciting opportunity to gather, in one supplement, a wide range of timely reports in the field of

neurovirology that will be of interest to the readers of the Journal of Neuroimmune Pharmacology. The goal of this supplement is to provide current, up-to-date information in a variety of virus–host systems and to define the important questions and new avenues of investigation and therapeutic development for viral infections of the CNS. Both basic and clinical researchers will benefit from the extensive reviews and primary research articles presented here. We are pleased to present a compilation of articles with the depth and breadth contained in this special issue and thank each of the contributors for their thoughtful submissions.

Acknowledgments We thank Howard E. Gendelman, Editor-in-Chief, and Robin Taylor, Managing Editor, for their assistance in preparing this special issue. SSS is supported by PHS grant 1R01AI074626-01. The authors declare that they have no conflicts of interest.

References

Ascherio A, Munger KL (2010) Epstein–Barr virus infection and multiple sclerosis: a review. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9201-3

Bender SJ, Weiss SR (2010) Pathogenesis of murine Coronavirus in the central nervous system. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9202-2

Christensen T (2010) HERVs in Neuropathogenesis. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9214-y

Gorantla S, Makarov E, Roy D, Finke-Dwyer J, Murrin LC, Gendelman HE, Poluektova L (2010) Immunoregulation of a CB2 receptor agonist in a murine model of neuroAIDS. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9225-8

Hollidge BS, Gonzalez-Scarano F, Soldan SS (2010) Arboviral encephalitides: transmission, emergence, and pathogenesis. J Neuroimmune Pharmacol, 5. doi:10.1007/s11481-010-9234-7

Kang SS, McGavern DB (2010) Microbial induction of vascular pathology in the CNS. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9208-9

Lindl KA, Marks DR, Kolson DL, Jordan-Sciutto KL (2010) HIV-associated neurocognitive disorder: pathogenesis and therapeutic opportunities. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9205-z

Marshall LJ, Major EO (2010) Molecular regulation of JC virus tropism: insights into potential therapeutic targets for progressive multifocal leukoencephalopathy. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9203-1

Matsuura E, Yamano Y, Jacobson S (2010) Neuroimmunity of HTLV-I infection. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9216-9

O'Donnell LA, Rall GF (2010) Blue moon Neurovirology: the merits of studying rare CNS diseases of viral origin. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9200-4

Saddawi-Konefka R, Crawford JR (2010) Chronic viral infection and primary central nervous system malignancy. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9204-0

Shah S, Nonnemacher MR, Pirrone V, Wigdahl B (2010) Innate and adaptive factors regulating human immunodeficiency virus type 1 genomic activation. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9207-x

Szpara ML, Kobiler O, Enquist LW (2010) A common neuronal response to alphaherpesvirus infection. J Neuroimmune Pharmacol. doi:10.1007/s11481-010-9212-0

Tsunoda I, Fujinami RS (2009) Neuropathogenesis of Theiler's murine encephalomyelitis virus infection, an animal model for multiple sclerosis. J Neuroimmune Pharmacol. doi:10.1007/s11481-009-9179-x

Yao K, Graham J, Akahata Y, Oh U, Jacobson S (2010) Mechanism of neuroinflammation: enhanced cytotoxicity and IL-17 production via CD46 binding. J Neuroimmune Pharmacol 5. doi:10.1007/s11481-010-9232-9