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Chapter VII

Role of Astrocytes in Viral Infections

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Abstract

Viral encephalitis is most commonly caused by neurotropic herpesviruses, enteroviruses, arboviruses, paramyxoviruses, rhabdoviruses and retroviruses. Astrocytes are a major cell population of the central nervous system (CNS) and play multiple roles in CNS development, function and responses to injury. Reactive astrocytes or astrogliosis is prominent in most CNS infections. Together with activated microglia, they play major roles in inflammatory and immune responses during viral infection. Activated astrocytes express toll-like receptors crucial for the induction of innate immune responses, including the secretion of chemokines or cytokines in response to virus agents. Astrocytes also express class II major histocompatibility complex antigens, but its role as an antigen-presenting cell is still controversial. Both protective and detrimental roles have been assigned to astrogliosis during viral infections. This chapter will summarize the role of astrocytes in CNS viral infections.

Introduction

Several viruses have adopted different strategies to successfully bypass the blood brain barrier (BBB) and enter into the central nervous system (CNS) cells to cause several inflamematory diseases such as meningitis, encephalitis or meningoencephalitis. The symptoms may vary and most of these neurotropic viruses may either produce severe damages, remain latent

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for long periods, or they can be reactivated to cause severe brain pathologies. Several viruses are capable to infect astrocytes, the most abundant CNS cell type. Since astrocytes play a crucial role in many normal CNS functions, infection of these cells may compromise such functions leading to serious CNS damages and neurological complications. Together with microglia, astrocytes have been involved to participate in both the innate and adaptive immune response to viral infectious agents. Reactive astrocytes can express many pattern recognition molecules as toll-like receptors and secret chemokines and cytokines. Moreover, although their role as antigen-presenting cells is still under discussion, reactive astrocytes may also express class II and class I major histocompatibility complex antigens as well as B-7 and B-40 co-stimulatory molecules. In the present chapter, we will discuss the role of astrocytes during CNS viral infection, focusing on their ability to exert both an innate or adaptive immune response. The protective and detrimental role assigned to astrocyte activation process during viral infections is another conflicting aspect that will be examined in this chapter.

Viral Infections of the Central Nervous System

Many viruses from different families are called neurotropic for their propensity to infect CNS cells and cause several diseases, including meningitis, encephalitis and meningoencephalitis (see Table 1). Encephalitis is an inflammation of the parenchyma, while meningitis is an inflammation of the leptomeninges. Although these infections may occur together and the spectrum of agents and syndromes overlap, in this chapter we will focus on viral encephalitis.

Viral encephalitis is most commonly caused by herpesviruses, enteroviruses, arboviruses, paramyxoviruses, rhabdoviruses and retroviruses (Griffin, 2003; Johnson, 2003). CNS viral infections may manifest acute, latent or chronic pathology. Viral strain and titer, route of infection, host's age and genetic background (van den Pol, 2009), as well as the extent of CNS injury due to virus-induced neuronal or glial cell death or secondary damage inflicted by immune mediators on infected cells are major factors affecting neuroinvasiveness, tropism, viral clearance or persistency. Most CNS infections present mild symptoms and subjects make a full recovery. Sometimes, however, viral encephalitis may be severe and associated with cell destruction, resulting in permanent brain damage or even death (Chakraborty et al., 2010).

Although herpesviruses (HHV) generally cause asymptomatic infections in humans, they can cause fatal CNS infections in immunocompromised subjects (Griffin, 2003). This is because, following primary exposure, HHV remains latent in the host cell nucleus and can be reactivated if host immune responses fail (Gilden et al., 2007). Herpes simplex virus type 1 and 2 are the etiological agents of acute and sometimes fatal encephalitis (Kleinschmidt-DeMasters and Gilden, 2001). They are capable of infecting not only neurons, but also microglia and astrocytes (Li et al., 2011a). Varicella-Zoster virus has been associated with myelitis, encephalitis and leukoencephalopathy (Gilden et al., 1998). For the Epstein-Barr virus, meningoencephalitis is a recognized complication of infectious mononucleosis, while the cytomegalovirus induces congenital infections associated with a variety of neurological disorders including encephalitis, a condition also observed in immunocompromised subjects

(Landolfo et al., 2003). Astrocytes are a main target and reservoir of HHV-6 in the CNS, which can cause encephalitis in both healthy and immunosuppressed patients (Donati et al., 2005; Johnson, 2003).

Table 1. Neurotropic viruses associated with human CNS disease

Virus	*Genus*	*Family*	*Genome*	*Cns disease*
HSV-1	Simplexvirus	Herpesviridae	*dsDNA*	Encephalitis
HSV-2				Encephalitis
VZV	Varicellovirus			Encephalitis, myelitis and leukoencephalo-pathy
EBV	Lymphocrypto-virus			Meningoence-phalitis
HCMV	Cytomegalovirus			Encephalitis
HHV-6	Roseolovirus			Encephalitis
JCV	Polyomavirus	Polyoma-viridae	dsDNA	Progressive Multifocal Leukoencephalo-pathy
Poliovirus	Enterovirus	Picornaviridae	+ssRNA	Poliomyelitis, encephalitis
Coxsackie-virus				Encephalitis, mild meningitis
ECHO				Encephalitis, mild meningitis
EEE Virus†	Alphavirus	Togaviridae	+ssRNA	Mild to fatal encephalitis, hemorrhagic syndrome
WEE Virus†				May be severe in neonates
VEE Virus†				Mild to fatal encephalomyeli-tis
La Crosse†	Orthobunyavirus	Bunyaviridae		Encephalitis
JEV†	Flavivirus	Flaviviridae		Encephalitis
WNV†				Encephalitis, meningitis and acute flaccid paralysis
Saint Louis†				Mild to severe encephalitis
LCMV	Arenavirus	Arenaviridae	-ssRNA	Meningoencephalitis
JUNV				Meningoencephalitis
MACV				Meningoencephalitis
NiV	Henipavirus	Paramyxo-viridae	-ssRNA	Febrile encephalitis
Measles Virus	Morbillivirus			Meningoencephalitis
Mumps Virus	Rubulavirus			Meningoencephalitis, aseptic meningitis
Rabies Virus	Lyssavirus	Rhabdoviridae	-ssRNA	Acute encephalitis
HIV	Lentivirus	Retroviridae	+ssRNA (RT)	Acute or chronic meningitis and encephalitis
HTLV-1	Deltaretrovirus			Tropical Spastic Paraparesis / HTLV associated myelopathy
HTLV-2				Subacute myelopathy

† Arbovirus; HSV: Herpes simplex virus; VZV: Varicella-Zoster virus; EBV: Epstein-Bar virus; HCMV: Human cytomegalovirus; HHV-6: Human herpes virus-6; EEE: Eastern equine encephalitis virus; WEE: Western equine encephalitis virus; VEE: Venezuelan equine encephalitis virus; JEV: Japanese encephalitis virus; WNV: West Nile encephalitis virus; LCMV: Lymphocytic choriomeningitis virus; JUNV: Junin virus; MACV: Machupo virus; NiV: Nipah virus; HIV: Human immunodeficiency virus; HTLV: Human T- lymphotropic virus.

The JC virus or John Cunningham virus (JCV), a human polyomavirus that also remains latent, is selective for astrocytes and oligodendrocytes and following reactivation by immunosuppression, elicits a lytic infection and causes progressive multifocal leukoencephalitis (Seth et al., 2004). Usually, enteroviruses, including polioviruses (PV), coxsackieviruses and echoviruses, cause mild meningitis, but sometimes may induce acute encephalitis. PV particularly targets the alpha motor neuron of the anterior horn of the spinal cord and causes poliomyelitis (Rhoades et al., 2011). Neurotropic arboviruses are an extensive group of viruses from the *Flaviviridae*, *Togaviridae* and *Bunyaviridae* families transmitted by arthropods or insects to humans, and can cause mild to fatal encephalitis

(Hollidge et al., 2010). Among them are the eastern equine encephalitis virus (EEEV), the Saint Louis encephalitis virus (SLEV), the La Crosse encephalitis virus (LACV), the western equine encephalitis virus (WEEV), the Japanese encephalitis virus (JEV) and the West Nile encephalitis virus (WNV)(Hollidge et al., 2010; McGavern and Kang, 2011; Schoneboom et al., 1999). Although they are usually associated with viral hemorrhagic fevers, many members of the *Arenaviridae* family can cause neurological disease in humans, including the lymphocytic choriomeningitis virus (LCMV), the Junin virus (JUNV) and the Machupo virus (MACV) (Gómez et al., 2011).

The Nipah virus (NiV), a highly virulent henipavirus of the *Paramyxoviridae* family, may induce severe neurological manifestations, including encephalitis (Johnson, 2003). Measles and mumps viruses, the other members of the *Paramyxoviridae* family, are known to present symptoms such as meningitis and encephalitis (Palacios et al., 2005). However, these neurological diseases are limited to complications of the normal course of the viral infection, with the exception of the rare and fatal subacute sclerosing panencephalitis (Manning et al., 2011). During the acute and fatal encephalitis produced by the rabies virus, a member of the *Rhabdoviridae* family, astrocytes are spared although the proliferation of uninfected reactive astrocytes is an inevitable result of rabies virus-associated encephalomyelitis (Griffin, 2003; Sofroniew and Vinters, 2010). Members of the *Retroviridae* family, such as the human immunodeficiency virus (HIV), can cause latent infection of CNS cells because of their capacity to integrate into the host genome (Lepoutre et al., 2009). Furthermore, the perpetuation strategies of retroviruses include oligoclonal proliferation within the cell that makes viral infection difficult to eradicate (Mortreux et al., 2001). Although HIV mainly targets $CD4^+$ T-cells, it is also a neurotropic virus that has been isolated from cerebrospinal fluid, spinal cord and brain. HIV entry into the CNS may result in several neurological manifestations including acute or chronic encephalitis (McArthur et al., 2005). HIV-1 can infect a small fraction of astrocytes *in vivo*, while productive infection of astrocytes with HIV-1 has significant effects on cell physiology *in vitro* (Cosenza-Nashat et al., 2006; Kim et al., 2004) and is associated with measurable neuropathology in mouse models (Dou et al., 2006). This suggests that infected astrocytes, although infrequent, can have localized pathogenic effects (Borjabad et al., 2010). Astrocyte dysfunction is regarded as the most likely mechanism mediating HIV-related cognitive impairment and neurodegeneration (Wang et al., 2004). HTLV-1 is a T-lymphotropic retrovirus that has been implicated in a distinct neurological disorder termed tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM), a chronic and progressive debilitating disease of the CNS with particular damage of the corticospinal tracts. TSP/HAM is characterized by an intense proliferation of chronically activated circulating cytotoxic T lymphocytes (CTL)(Mahieux and Gessain, 2007). HTLV-1-infected T lymphocytes impair catabolism and uptake of glutamate in astrocytes via Tax-1 and tumor necrosis factor α (TNF-α)(Szymocha et al., 2000).

Many animal viruses that result in chronic infections of the CNS have been extensively used as models for examining various pathogenic mechanisms, including the roles of astrocyte. Neurons are the main targets in the murine CNS for many kinds of viruses, including Sindbis virus (SINV), a member of the alphaviruses used as a model system for studying viral encephalitis, JEV, WNV, VSV, LCMV and JUNV (Chakraborty et al., 2010; Gómez et al., 2011; Kang and McGavern, 2008). Viruses that cause chronic infection along with myelin loss include the picornavirus Theiler's murine encephalomyelitis virus (TMEV)(Jakob and Roos, 1996), where astrocytes are the major viral reservoirs (Zheng et al.,

2001), the coronavirus mouse hepatitis virus (MHV)(Bergmann et al., 2006) and the paramyxovirus canine distemper virus (CDV)(Wyss-Fluehmann et al., 2010). Finally, experimental rat infections with the Borna disease virus (BDV) have extensively been used to explore viral-induced psychiatric diseases (Ludwig and Bode, 2000).

Astrocytes Are Activated during Viral Infection

Astrocytes are the most abundant cells in the CNS and increasing evidence points towards their functional heterogeneity from different regions of the CNS (Yeh et al., 2009). In general, they are involved in the regulation of the CNS microenvironment, metabolic support of neurons, synaptic transmission, neurotropism, detoxification, development and maintenance of the BBB, guidance of neuronal migration during development, and several inflammatory and immune functions (Norenberg, 2005; Sidoryk-Wegrzynowicz et al., 2011; Sofroniew and Vinters, 2010).

In several, if not all, forms of CNS injury, including viral CNS infections, astrocytes undergo a dramatic transformation referred to as reactive astrocytosis or astrogliosis (Norenberg, 2005; Sofroniew, 2009). Astrogliosis vary with the nature and severity of the insult in terms of a graduated continuum of progressive alterations in molecular expression, progressive cellular hypertrophy and, in severe cases, proliferation and scar formation (Sofroniew, 2009). It should be differentiated from gliosis or reactive gliosis, which is also frequent in viral infections and includes other cells besides astrocytes such as microglia, macrophages, oligodendroglial progenitor cells, meningeal cells and mesenchymal elements (Norenberg, 2005). When the injury is focal but includes significant necrosis, astrogliosis usually occurs at the margin rather than at the cavitated center of the lesion. Depending on the distance from the lesion, two electrophysiologically, immunohistochemically and morphologically distinct types of hypertrophied astrocytes may be found (Anderova et al., 2001). If the lesion is relatively small, the cavitation it could be fulfilled by reactive astrocytes. In viral infections of the CNS without a cavitary component, astrogliosis may be disseminated (Norenberg, 2005) of the isomorphic type (Fernaud-Espinosa et al., 1993).

Reactive astrocytes exhibit hypertrophy with cytoplasmic processes that are more numerous, longer and thicker. These correlate with an enhanced expression of many proteins, most notably the components of the 10-nm intermediate filaments of the cytoskeleton glial fibrillary acid protein (GFAP)(Eng et al., 2000), vimentin (Lazarides, 1982) and nestin (Lendahl et al., 1990), the last two being expressed only during development and not in most adult astrocytes. Glial activation during CNS viral infection may be triggered in several ways, such as direct viral infection, released viral particles, viral proteins, dsRNA, viral replication and neuronal cell death, as well as other immune challenges (Chen et al., 2010). It is accepted that microglia plays a critical role in the induction of reactive astrogliosis (Giulian et al., 1994; Zhang et al., 2010). Their release of several proinflammatory molecules, including the cytokines interleukin 1 (IL-1), IL-6, TNF-α and IFN-γ, favor astrogliosis, while IL-10 diminishes their extension (Yong, 1996). Many other molecules such as growth factors, neurotransmitters, products associated with neurodegeneration (e.g., prion proteins) and regulators of cell proliferation (e.g., endothelin-1) have been proposed as triggers of astrogliosis (Norenberg, 2005; Sofroniew and Vinters, 2010). Interesting, studies in

transgenic mice have revealed that the activation of the endogenous GFAP gene as a consequence of viral infection could involve different regulatory pathways other than activation as a result of prion infection (Titeux et al., 2002). In this regard, a major role in the induction of GFAP has been assigned to nitric oxide (NO)(Brahmachari et al., 2006). Since the inducible form of NO synthase (iNOS), the isoform that produces the highest levels of NO, may be induced by several molecules mentioned above produced by activated microglia and astrocytes (Hewett et al., 1993), it is plausible that NO derived from iNOS might be a relevant mediator of astrocyte activation in processes such as viral infections (Akaike and Maeda, 2000; Munoz-Fernandez and Fresno, 1998; Saha and Pahan, 2006).

Astrogliosis is clearly detected approximately 7 to 10 days after an acute injury, with a peak at 14 to 21 days and a variable time of regression (Norenberg, 2005). In viral infections, it has been observed over much longer periods and may be related to the elimination of the etiologic trigger (Caccuri et al., 2003; Mrak and Griffin, 1997; Wyss-Fluehmann et al., 2010). Reactive astrocytes seem to revert to a more immature stage (Norenberg, 2005; Pekny, 2001). As mentioned before, reactive astrocytes express nestin, vimentin and tenascin-C as well as the neuronal markers MAP-2 (Lin and Matesic, 1994), GABA (Lin et al., 1993), neuron-specific enolase (Lin and Matesic, 1994) and calbindin-D28K (Freund et al., 1990).

Reactive astrocytes show enhanced expression of ion channels (K^+, Ca^{++}) (Westenbroek et al., 1998), the glutamate transporters GLT-1 and GLAST (Anderson and Swanson, 2000), and the glucose transporter GLUT1 (Norenberg, 2005). They also display gap junctions in their membranes (Landis and Reese, 1981), a fact that could be important in the spreading of viral infections by cell-to-cell transmission. In addition to the mentioned molecules, reactive astrocytes produce a plethora of factors, including enzymes, growth factors, cytokines, extracellular matrix components, protease inhibitors, proto-oncogenes, heat-shock proteins and galectins among many others (Jeon et al., 2010; Norenberg, 2005). Another interesting aspect of astrogliosis is the potential of stem cell production following brain injury, because some astrocytes labeled before injury acquire the capacity to form multipotent and self-renewing neurospheres and may act as a promising source of multipotent cells within the injury site that may be particularly suited to elicit neuronal repair in brain regions far away from zones of adult neurogenesis (Robel et al., 2011). However, the role and utility of such an event in viral infections is still completely unknown.

Role of Astrocytes in the Innate Viral Immune Response

The absence of lymphatic irrigation, the low levels of major histocompatibility complex (MHC) molecules and the presence of a BBB all enable the CNS to be an immune-privileged organ system (Galea et al., 2007). Astrocyte foot processes are in close opposition to the abluminal surface of the microvascular endothelium of the BBB; thus, astrocytes contribute to both the structural and functional integrity of the BBB (Dong and Benveniste, 2001). In the uninfected CNS, astrocytes and meningeal cells suppress activation of the surrounding cells by producing the anti-inflammatory cytokine transforming growth factor-β (TGF-β)(Griffin, 2003). Toll-like receptors (TLR) 3, 7, 8 and 9 are engaged in viral pathogen-associated molecular pattern recognition and at least TLR 3, 7 and 9 are expressed in activated microglia

and astrocytes (Bsibsi et al., 2002; Farina et al., 2005; McKimmie et al., 2005; Suh et al., 2009). They are crucial for the induction of innate and adaptive immune responses within the CNS to protect neuronal cells from invading viruses (Dong and Benveniste, 2001). For example, in human fetal astrocytes, activation of TLR3 by its ligand poly I:C activates more than 1,000 genes including the interferon (IFN)-stimulated genes (ISG)(Rivieccio et al., 2006). Poly I:C-conditioned medium, but not LPS-conditioned medium, promotes the survival of neurons in organotypic human brain slice cultures, implying that TLR3, but not TLR4, binding may elicit neuroprotective gene expression in astrocytes (Bsibsi et al., 2006). In addition, TMEV infection induces TLR3-dependent up-regulation of TLR2, which is critical for the production of proinflammatory molecules (So and Kim, 2009). The production of chemokines in the brain parenchyma acts as a signal to attract pathogen-specific $CD4^+$ and $CD8^+$ T-cells to the CNS and therefore, contributes to the immune-mediated adaptive response to control infection (Kamperschroer and Quinn, 2002). Some studies have also suggested that inappropriate activation of TLR can result in a pathogenic outcome rather than a protective one. Since TLR ligands are actively considered for their antiviral and potential adjuvant effects, this will be an important issue to address in the context of the CNS environment (Suh et al., 2009).

After viral infection of the CNS, a rapid production of type I interferon (IFN I) is critical to inhibit viral spread (Griffin, 2003). Cultured astrocytes infected by TMEV can trigger IFN-α synthesis (So and Kim, 2009). However, in experimental CNS infection by MHV, the main IFN I produced in the CNS is IFN-β, which is produced by macrophages and microglia, but not by neurons or astrocytes (Roth-Cross et al., 2008). This is particularly relevant because preferential production of IFN-β rather than IFN-α is associated with both anti-inflammatory and neuroprotective responses. The anti-inflammatory response, either by direct action or through the induction of anti-inflammatory cytokines such as IL-10, is exerted by down-regulating the expression of molecules such as MHC class II and co-stimulatory molecules, or adhesion molecules, chemokines and matrix metalloproteinases that modulate antigen presentation and trafficking of inflammatory cells into the CNS, respectively (Yong, 2002). The neuroprotective action of IFN-β is less clear and has been associated with either the direct action or through the induction of neurotropic factors (Kieseier and Hartung, 2007). In both the anti-inflammatory and neuroprotective responses, astrocytes have been assigned a critical role (Kieseier and Hartung, 2007; Yong, 2002).

Role of Astrocytes in the Adaptive Viral Immune Response

Under viral infections, different leukocytes including lymphocytes are capable of invading the CNS. Astrocytes, given their strategic position in the BBB, play a crucial role in limiting the entry of different immune cell subsets into the CNS (Ambrosini et al., 2005). The expression of MHC class II molecules is necessary to induce immune responses through presenting processed antigens to $CD4^+$ T-helper cells. Although MHC class II molecules are usually expressed by specialized antigen-presenting cells (APC) such as B cells, macrophages and dendritic cells, expression on other cell types can be induced by cytokines such as IFN-γ (Dong and Benveniste, 2001). Reactive astrocytes can express class I (Suzumura et al., 1986)

and class II (Frank et al., 1986) MHC molecules. Intrathecal injection of IFN-γ induces class II MHC expression in astrocytes, although expression is less intense and occurs later than in microglia (Vass and Lassmann, 1990). Reactive astrocytes also express co-stimulatory molecules B7 and CD40 that are critical for antigen presentation and T-cell activation (Tan et al., 1998) and several studies have showed that reactive astrocytes can effectively process and present antigens to $CD4^+$ T-helper cells (Seth and Koul, 2008), thus maintaining activated Th1 and Th17 cells (Constantinescu et al., 2005). These results led to the proposal that astrocytes function as APC. However, by contrast, other studies in human astrocytes have not found any evidence of expression of CD80 (B7-1), CD86 (B7-2) or CD40 co-stimulating signal molecules (Dong and Benveniste, 2001; Satoh et al., 1995; Windhagen et al., 1995), making the role of astrocytes as APC unclear. Currently, although still controversial, it is proposed that astrocytes may act as APC, but lesser efficiently than microglia (Chastain et al., 2011). The expression of the chemokine CXCL10, associated with the severity of LCMV-induced disease, initially depends on signaling through the IFN I receptor by resident cells, while late expression and up-regulation requires IFN II produced by the recruited $CD8^+$ T-cells. Throughout LCMV infection, the producers of CXCL10 are exclusively resident cells of the CNS, and astrocytes, not microglial cells, are the dominant producers in the neural parenchyma. Based on these results, a model of bidirectional interplay between resident cells of the CNS and the recruited virus-specific T cells with astrocytes as active participants in the local antiviral host response have been suggested (Christensen et al., 2009). Perhaps more studies based on this bidirectional interplay may help to elucidate the *in vivo* role of astrocytes as APC in CNS viral infection.

Significance of Astrocyte Activation in Viral Infections

The significance of astrogliosis is still unclear (Norenberg, 2005). On one hand, it is generally accepted that reactive astrocytes are beneficial since they exert vital functions that are altered during injury, including restoration of the extracellular microenvironment by removing toxic molecules such as glutamate and free radicals and restoring the BBB (Ridet et al., 1997). They may also participate in axonal and neurite growth by synthesizing several growth factors and extracellular matrix components to facilitate repair and regeneration (Buffo et al., 2008; Norenberg, 2005; Ridet et al., 1997; Sofroniew and Vinters, 2010). This concept is supported by many non-viral and viral studies. In pioneering studies carried out in adult mice expressing HSV-TK under the GFAP promoter and treated with ganciclovir to selectively suppress reactive astrocytes adjacent to a forebrain stab injury, a prolonged infiltration of leukocytes, failure of BBB repair, extensive glutamate-mediated neuronal degeneration and a pronounced increase in local neurite outgrowth was observed, showing a more beneficial than detrimental role of astrogliosis (Bush et al., 1999). Moreover, inhibition of reactive astrocytosis by inducing experimental autoimmune encephalomyelitis (EAE) leads to increased macrophage, but not T cell, infiltration and enhanced severity of EAE (Toft-Hansen et al., 2011). Relatively similar results were found in mice genetically deficient in GFAP and vimentin after a traumatic injury where intermediate filaments of reactive astrocytes were required for proper organization of post-traumatic glial scars (Pekny, 2001).

In JUNV-induced encephalitis and despite heavy infection of neural structures, neurons do not usually show major changes. By contrast, a severe astrocyte reaction is present, showing enhanced expression of GFAP (Lascano and Berria, 1983), iNOS, mitochondrial superoxide dismutase (Gomez et al., 2003) and galectin-3 (Giusti et al., 2011). In chronically infected animals, no correlation between viral antigen and reactive astrocyte distribution has been observed (Lascano et al., 1989). Evidence of a protective role for enhanced NO production is thought not to be related to reduced viral replication but rather to enhanced astrocyte activation, suggesting that this behavior may represent a beneficial cell response to virus-induced CNS damage (Gomez et al., 2003). In HIV-related CNS disease, the protective role of astrocytes seems to be complex. HIV-1 neuroinvasion occurs early (during the period of initial viremia), leading to infection of a limited number of susceptible cells with low CD4 expression. Activation of microglia and astrocytes, due to local or peripheral triggers, increases chemokine production, enhances traffic of infected cells into the CNS and significantly augments the spread of viral species (Persidsky and Poluektova, 2006). The mechanism of HIV-mediated neurologic disorders is not entirely clear, but it is likely to be driven by both direct (active viral replication) and indirect effects of HIV invasion of the brain. Indirect mechanisms include dysregulation of glia, release of viral proteins and elevation of neurotoxic proteins (TNF-α, IL-6, IL-1b, TGF-β, endothelin and glutamate) from resident brain cells and infiltrating lymphocytes (Li et al., 2011b). Glutamate toxicity acts via two distinct pathways: an excitotoxic one, in which glutamate receptors are hyperactivated, and an oxidative one, in which cysteine uptake is inhibited, resulting in glutathione depletion, oxidative stress and cell degeneration. A number of studies have shown that astrocytes normally take up glutamate, keeping extracellular glutamate concentration low in the brain and preventing excitotoxicity. Astrocytes also provide the trophic amino acid glutamine via their expression of glutamine synthetase. These protective and trophic actions are inhibited in HIV infection, probably as a result of the effects of inflammatory mediators and viral proteins (Gras et al., 2006).

On the other hand, astrogliosis can be viewed as detrimental for neuronal function and regeneration by the formation of glial scars (Chvatal et al., 2008; Dong and Benveniste, 2001). In fact, various regeneration inhibitory molecules are synthesized by reactive astrocytes including tenascin-C, chondroitin sulfate proteoglycan, NG2-proteoglycan, matrix metalloproteinases (MMP) and other mechanisms that are not yet fully understood (Chen et al., 2010; Fawcett and Asher, 1999).

It has been demonstrated that WNV infection in astrocytes elicits multiple MMP, which disrupts the BBB, as well as cyclooxygenase enzymes that, by their product prostaglandin E2, regulates the production of multiple inflammatory molecules (Verma et al., 2011). Neuronal apoptosis occurs not only in areas of CNS positive for VEE-antigen, but also in areas of astrogliosis. These findings suggest that the inflammatory response, which is in part mediated by iNOS and TNF-α, may contribute to neurodegeneration following encephalitic viral infection (Schoneboom et al., 2000). In the same line, since TMEV infection of cultured astrocytes induces proinflammatory cytokines, a contribution of activated astrocytes to TMEV-induced demyelinating disease has been proposed (Palma et al., 2003). Moreover, SINV infection leads to changes characteristic of astrogliosis and this reaction has been associated with the pathogenesis of SINV-induced encephalitis by enhancing the local immune response in the CNS (Brodie et al., 1997). Indirect mechanisms have also been implicated. Activated astrocytes are potent producers of IL-6 in the diseased CNS (Dong and

Benveniste, 2001). IL-6 is induced in the brain later than IFN-γ and IL-1 following LCMV infection of mice, consistent with IL-6 exerting its major effect later in the infection course, which contributes to the neurodegenerative signs present in the chronic disease (Kamperschroer and Quinn, 2002).

Conclusion

Although significant progress has been made in recent years to better understand astrogliosis, the most common and ubiquitous response to CNS injury, the role of astrogliosis in CNS viral infections is still not known. Bearing in mind the contradictory roles of vital or detrimental assigned to it, much more information is still critically needed. Moreover, future studies should include the complex influence of neurons, astrocytes and microglia and vice versa *in vivo* (Rock et al., 2004).

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References

Akaike, T., and Maeda, H. (2000). Nitric oxide and virus infection. *Immunology* 101, 300-308.

Ambrosini, E., Remoli, M. E., Giacomini, E., Rosicarelli, B., Serafini, B., Lande, R., Aloisi, F., and Coccia, E. M. (2005). Astrocytes produce dendritic cell-attracting chemokines in vitro and in multiple sclerosis lesions. *J Neuropathol Exp Neurol* 64, 706-715.

Anderova, M., Kubinova, S., Mazel, T., Chvatal, A., Eliasson, C., Pekny, M., and Sykova, E. (2001). Effect of elevated K(+), hypotonic stress, and cortical spreading depression on astrocyte swelling in GFAP-deficient mice. *Glia 35*, 189-203.

Anderson, C. M., and Swanson, R. A. (2000). Astrocyte glutamate transport: review of properties, regulation, and physiological functions. *Glia 32*, 1-14.

Bergmann, C. C., Lane, T. E., and Stohlman, S. A. (2006). Coronavirus infection of the central nervous system: host-virus stand-off. *Nat Rev Microbiol* 4, 121-132.

Borjabad, A., Brooks, A. I., and Volsky, D. J. (2010). Gene expression profiles of HIV-1-infected glia and brain: toward better understanding of the role of astrocytes in HIV-1-associated neurocognitive disorders. *J Neuroimmune Pharmacol 5*, 44-62.

Brahmachari, S., Fung, Y. K., and Pahan, K. (2006). Induction of glial fibrillary acidic protein expression in astrocytes by nitric oxide. *J Neurosci 26*, 4930-4939.

Brodie, C., Weizman, N., Katzoff, A., Lustig, S., and Kobiler, D. (1997). Astrocyte activation by Sindbis virus: expression of GFAP, cytokines, and adhesion molecules. *Glia* 19, 275-285.

Bsibsi, M., Persoon-Deen, C., Verwer, R. W., Meeuwsen, S., Ravid, R., and Van Noort, J.M. (2006). Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators. *Glia* 53, 688-695.

Bsibsi, M., Ravid, R., Gveric, D., and van Noort, J. M. (2002). Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* 61, 1013-1021.

Buffo, A., Rite, I., Tripathi, P., Lepier, A., Colak, D., Horn, A. P., Mori, T., and Gotz, M. (2008). Origin and progeny of reactive gliosis: A source of multipotent cells in the injured brain. *Proc Natl Acad Sci USA* 105, 3581-3586.

Bush, T. G., Puvanachandra, N., Horner, C. H., Polito, A., Ostenfeld, T., Svendsen, C. N., Mucke, L., Johnson, M. H., and Sofroniew, M. V. (1999). Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron* 23, 297-308.

Caccuri, R. L., Iacono, R. F., Weissenbacher, M. C., Avila, M. M., and Berria, M. I. (2003). Long-lasting astrocyte reaction to persistent Junin virus infection of rat cortical neurons. *J Neural Transm* 110, 847-857.

Chakraborty, S., Nazmi, A., Dutta, K., and Basu, A. (2010). Neurons under viral attack: victims or warriors? *Neurochem Int* 56, 727-735.

Chastain, E. M., Duncan, D. S., Rodgers, J. M., and Miller, S. D. (2011). The role of antigen presenting cells in multiple sclerosis. *Biochim Biophys Acta* 1812, 265-274.

Chen, C. J., Ou, Y. C., Lin, S. Y., Raung, S. L., Liao, S. L., Lai, C. Y., Chen, S. Y., and Chen, J. H. (2010). Glial activation involvement in neuronal death by Japanese encephalitis virus infection. *J Gen Virol* 91, 1028-1037.

Christensen, J. E., Simonsen, S., Fenger, C., Sorensen, M. R., Moos, T., Christensen, J. P., Finsen, B., and Thomsen, A. R. (2009). Fulminant lymphocytic choriomeningitis virus-induced inflammation of the CNS involves a cytokine-chemokine-cytokine-chemokine cascade. *J Immunol* 182, 1079-1087.

Chvatal, A., Anderova, M., Neprasova, H., Prajerova, I., Benesova, J., Butenko, O., and Verkhratsky, A. (2008). Pathological potential of astroglia. *Physiol Res* 57 Suppl 3, S101-110.

Constantinescu, C. S., Tani, M., Ransohoff, R. M., Wysocka, M., Hilliard, B., Fujioka, T., Murphy, S., Tighe, P. J., Das Sarma, J., Trinchieri, G. et al. (2005). Astrocytes as antigen-presenting cells: expression of IL-12/IL-23. *J Neurochem* 95, 331-340.

Cosenza-Nashat, M. A., Si, Q., Zhao, M. L., and Lee, S.C. (2006). Modulation of astrocyte proliferation by HIV-1: differential effects in productively infected, uninfected, and Nef-expressing cells. *J Neuroimmunol* 178, 87-99.

Donati, D., Martinelli, E., Cassiani-Ingoni, R., Ahlqvist, J., Hou, J., Major, E.O., and Jacobson, S. (2005). Variant-specific tropism of human herpesvirus 6 in human astrocytes. *J Virol* 79, 9439-9448.

Dong, Y., and Benveniste, E.N. (2001). Immune function of astrocytes. *Glia* 36, 180-190.

Dou, H., Morehead, J., Bradley, J., Gorantla, S., Ellison, B., Kingsley, J., Smith, L. M., Chao, W., Bentsman, G., Volsky, D. J. et al. (2006). Neuropathologic and neuroinflammatory activities of HIV-1-infected human astrocytes in murine brain. *Glia* 54, 81-93.

Eng, L. F., Ghirnikar, R. S., and Lee, Y. L. (2000). Glial fibrilary acidic protein: GFAP-thirty-one years (1969-2000). *Neurochemical Research* 25, 1439-1451.

Farina, C., Krumbholz, M., Giese, T., Hartmann, G., Aloisi, F., and Meinl, E. (2005). Preferential expression and function of Toll-like receptor 3 in human astrocytes. *J Neuroimmunol* 159, 12-19.

Fawcett, J. W., and Asher, R. A. (1999). The glial scar and central nervous system repair. *Brain Res Bull* 49, 377-391.

Fernaud-Espinosa, I., Nieto-Sampedro, M., and Bovolenta, P. (1993). Differential activation of microglia and astrocytes in aniso- and isomorphic gliotic tissue. *Glia 8*, 277-291.

Frank, E., Pulver, M., and de Tribolet, N. (1986). Expression of class II major histocompatibility antigens on reactive astrocytes and endothelial cells within the gliosis surrounding metastases and abscesses. *J Neuroimmunol* 12, 29-36.

Freund, T. F., Buzsaki, G., Leon, A., Baimbridge, K.G., and Somogyi, P. (1990). Relationship of neuronal vulnerability and calcium binding protein immunoreactivity in ischemia. *Exp Brain Res* 83, 55-66.

Galea, I., Bechmann, I., and Perry, V. H. (2007). What is immune privilege (not)? *Trends Immunol* 28, 12-18.

Gilden, D. H., Bennett, J. L., Kleinschmidt-De Masters, B. K., Song, D. D., Yee, A. S., and Steiner, I. (1998). The value of cerebrospinal fluid antiviral antibody in the diagnosis of neurologic disease produced by varicella zoster virus. *J Neurol Sci* 159, 140-144.

Gilden, D. H., Mahalingam, R., Cohrs, R. J., and Tyler, K. L. (2007). Herpesvirus infections of the nervous system. *Nat Clin Pract Neurol* 3, 82-94.

Giulian, D., Li, J., Li, X., George, J., and Rutecki, P. A. (1994). The impact of microglia-derived cytokines upon gliosis in the CNS. *Dev Neurosci* 16, 128-136.

Giusti, C. J., Alberdi, L., Frik, J., Ferrer, M. F., Scharrig, E., Schattner, M., and Gómez, R.M. (2011). Galectin-3 is upregulated in activated glia during Junín virus-induced murine encephalitis. *Neurosci Lett* 501, 163-166.

Gómez, R. M., Jaquenod de Giusti, C., Sanchez Vallduvi, M. M., Frik, J., Ferrer, M. F., and Schattner, M. (2011). Junín virus. A XXI century update. *Microbes Infect* 13, 303-311.

Gómez, R. M., Yep, A., Schattner, M., and Berria, M. I. (2003). Junín virus-induced astrocytosis is impaired by iNOS inhibition. *J Med Virol* 69, 145-149.

Gras, G., Porcheray, F., Samah, B., and Leone, C. (2006). The glutamate-glutamine cycle as an inducible, protective face of macrophage activation. *J Leukoc Biol* 80, 1067-1075.

Griffin, D. E. (2003). Immune responses to RNA-virus infections of the CNS. *Nat Rev Immunol* 3, 493-502.

Hewett, S. J., Corbett, J. A., McDaniel, M. L., and Choi, D. W. (1993). Interferon-gamma and interleukin-1 beta induce nitric oxide formation from primary mouse astrocytes. *Neurosci Lett* 164, 229-232.

Hollidge, B. S., Gonzalez-Scarano, F., and Soldan, S. S. (2010). Arboviral encephalitides: transmission, emergence, and pathogenesis. *J Neuroimmune Pharmacol 5*, 428-442.

Jakob, J., and Roos, R. P. (1996). Molecular determinants of Theiler's murine encephalo-myelitis-induced disease. *J Neurovirol* 2, 70-77.

Jeon, S. B., Yoon, H. J., Chang, C. Y., Koh, H. S., Jeon, S. H., and Park, E. J. (2010). Galectin-3 exerts cytokine-like regulatory actions through the JAK-STAT pathway. *J Immunol* 185, 7037-7046.

Johnson, R. T. (2003). Emerging viral infections of the nervous system. *J Neurovirol* 9, 140-147.

Kamperschroer, C., and Quinn, D. G. (2002). The role of proinflammatory cytokines in wasting disease during lymphocytic choriomeningitis virus infection. *J Immunol* 169, 340-349.

Kang, S. S., and McGavern, D. B. (2008). Lymphocytic choriomeningitis infection of the central nervous system. *Front Biosci* 13, 4529-4543.

Kieseier, B. C., and Hartung, H. P. (2007). Interferon-beta and neuroprotection in multiple sclerosis--facts, hopes and phantasies. *Exp Neurol* 203, 1-4.

Kim, S. Y., Li, J., Bentsman, G., Brooks, A. I., and Volsky, D. J. (2004). Microarray analysis of changes in cellular gene expression induced by productive infection of primary human astrocytes: implications for HAD. *J Neuroimmunol* 157, 17-26.

Kleinschmidt-DeMasters, B. K., and Gilden, D. H. (2001). The expanding spectrum of herpesvirus infections of the nervous system. *Brain Pathol* 11, 440-451.

Landis, D. M., and Reese, T. S. (1981). Membrane structure in mammalian astrocytes: a review of freeze-fracture studies on adult, developing, reactive and cultured astrocytes. *J Exp Biol* 95, 35-48.

Landolfo, S., Gariglio, M., Gribaudo, G., and Lembo, D. (2003). The human cytomegalovirus. *Pharmacol Ther* 98, 269-297.

Lascano, E. F., and Berria, M. I. (1983). Immunoperoxidase study of astrocytic reaction in Junín virus encephalomyelitis of mice. *Acta Neuropathol* 59, 183-190.

Lascano, E. F., Berria, M. I., Avila, M. M., and Weissenbacher, M. C. (1989). Astrocytic reaction predominance in chronic encephalitis of Junín virus-infected rats. *J Med Virol* 29, 327-333.

Lazarides, E. (1982). Intermediate filaments: a chemically heterogeneous, developmentally regulated class of proteins. *Annu Rev Biochem* 51, 219-250.

Lendahl, U., Zimmerman, L. B., and McKay, R. D. (1990). CNS stem cells express a new class of intermediate filament protein. *Cell* 60, 585-595.

Lepoutre, V., Jain, P., Quann, K., Wigdahl, B., and Khan, Z. K. (2009). Role of resident CNS cell populations in HTLV-1-associated neuroinflammatory disease. *Front Biosci* 14, 1152-1168.

Li, J., Hu, S., Zhou, L., Ye, L., Wang, X., Ho, J., and Ho, W. (2011a). Interferon lambda inhibits herpes simplex virus type I infection of human astrocytes and neurons. *Glia* 59, 58-67.

Li, W., Henderson, L. J., Major, E. O., and Al-Harthi, L. (2011b). IFN-gamma mediates enhancement of HIV replication in astrocytes by inducing an antagonist of the beta-catenin pathway (DKK1) in a STAT 3-dependent manner. *J Immunol* 186, 6771-6778.

Lin, R. C., and Matesic, D. F. (1994). Immunohistochemical demonstration of neuron-specific enolase and microtubule-associated protein 2 in reactive astrocytes after injury in the adult forebrain. *Neuroscience* 60, 11-16.

Lin, R. C., Polsky, K., and Matesic, D. F. (1993). Expression of gamma-aminobutyric acid immunoreactivity in reactive astrocytes after ischemia-induced injury in the adult forebrain. *Brain Res* 600, 1-8.

Ludwig, H., and Bode, L. (2000). Borna disease virus: new aspects on infection, disease, diagnosis and epidemiology. *Rev Sci Tech* 19, 259-288.

Mahieux, R., and Gessain, A. (2007). Adult T-cell leukemia/lymphoma and HTLV-1. Curr Hematol *Malig Rep* 2, 257-264.

Manning, L., Laman, M., Edoni, H., Mueller, I., Karunajeewa, H. A., Smith, D., Hwaiwhanje, I., Siba, P. M., and Davis, T. M. (2011). Subacute sclerosing panencephalitis in papua new guinean children: the cost of continuing inadequate measles vaccine coverage. *PLoS Negl Trop Dis 5*, e932.

McArthur, J. C., Brew, B. J., and Nath, A. (2005). Neurological complications of HIV infection. *Lancet Neurol* 4, 543-555.

McGavern, D. B., and Kang, S. S. (2011). Illuminating viral infections in the nervous system. *Nat Rev Immunol* 11, 318-329.

McKimmie, C. S., Johnson, N., Fooks, A. R., and Fazakerley, J. K. (2005). Viruses selectively upregulate Toll-like receptors in the central nervous system. *Biochem Biophys Res Commun* 336, 925-933.

Mortreux, F., Leclercq, I., Gabet, A.S., Leroy, A., Westhof, E., Gessain, A., Wain-Hobson, S., and Wattel, E. (2001). Somatic mutation in human T-cell leukemia virus type 1 provirus and flanking cellular sequences during clonal expansion in vivo. *J Natl Cancer Inst* 93, 367-377.

Mrak, R. E., and Griffin, W. S. (1997). The role of chronic self-propagating glial responses in neurodegeneration: implications for long-lived survivors of human immunodeficiency virus. *J Neurovirol* 3, 241-246.

Munoz-Fernandez, M. A., and Fresno, M. (1998). The role of tumour necrosis factor, interleukin 6, interferon-gamma and inducible nitric oxide synthase in the development and pathology of the nervous system. *Prog Neurobiol* 56, 307-340.

Norenberg, M. D. (2005). The reactive astrocyte. In The Role of Glia in Neurotoxicity, M. Aschner, and L. G. Costa, eds. (CRC), pp. 73-92.

Palacios, G., Jabado, O., Cisterna, D., de Ory, F., Renwick, N., Echevarria, J. E., Castellanos, A., Mosquera, M., Freire, M. C., Campos, R.H., et al. (2005). Molecular identification of mumps virus genotypes from clinical samples: standardized method of analysis. *J Clin Microbiol* 43, 1869-1878.

Palma, J. P., Kwon, D., Clipstone, N. A., and Kim, B. S. (2003). Infection with Theiler's murine encephalomyelitis virus directly induces proinflammatory cytokines in primary astrocytes via NF-kappaB activation: potential role for the initiation of demyelinating disease. *J Virol 77*, 6322-6331.

Pekny, M. (2001). Astrocytic intermediate filaments: lessons from GFAP and vimentin knock-out mice. *Progress in Brain Research* 132, 23-30.

Persidsky, Y., and Poluektova, L. (2006). Immune privilege and HIV-1 persistence in the CNS. *Immunol Rev* 213, 180-194.

Rhoades, R. E., Tabor-Godwin, J. M., Tsueng, G., and Feuer, R. (2011). Enterovirus infections of the central nervous system. *Virology* 411, 288-305.

Ridet, J. L., Malhotra, S. K., Privat, A., and Gage, F. H. (1997). Reactive astrocytes: cellular and molecular cues to biological function. *Trends Neurosci* 20, 570-577.

Rivieccio, M. A., Suh, H. S., Zhao, Y., Zhao, M. L., Chin, K. C., Lee, S. C., and Brosnan, C. F. (2006). TLR3 ligation activates an antiviral response in human fetal astrocytes: a role for viperin/cig5. *J Immunol* 177, 4735-4741.

Robel, S., Berninger, B., and Gotz, M. (2011). The stem cell potential of glia: lessons from reactive gliosis. *Nat Rev Neurosci* 12, 88-104.

Rock, R. B., Gekker, G., Hu, S., Sheng, W. S., Cheeran, M., Lokensgard, J. R., and Peterson, P. K. (2004). Role of microglia in central nervous system infections. *Clin Microbiol Rev* 17, 942-964, table of contents.

Roth-Cross, J. K., Bender, S. J., and Weiss, S. R. (2008). Murine coronavirus mouse hepatitis virus is recognized by MDA5 and induces type I interferon in brain macrophages/ microglia. *J Virol* 82, 9829-9838.

Saha, R. N., and Pahan, K. (2006). Regulation of inducible nitric oxide synthase gene in glial cells. *Antioxid Redox Signal* 8, 929-947.

Satoh, J., Lee, Y. B., and Kim, S. U. (1995). T-cell costimulatory molecules B7-1 (CD80) and B7-2 (CD86) are expressed in human microglia but not in astrocytes in culture. *Brain Res* 704, 92-96.

Schoneboom, B. A., Catlin, K. M., Marty, A. M., and Grieder, F. B. (2000). Inflammation is a component of neurodegeneration in response to Venezuelan equine encephalitis virus infection in mice. *J Neuroimmunol* 109, 132-146.

Schoneboom, B. A., Fultz, M. J., Miller, T. H., McKinney, L. C., and Grieder, F. B. (1999). Astrocytes as targets for Venezuelan equine encephalitis virus infection. *J Neurovirol 5*, 342-354.

Seth, P., Diaz, F., Tao-Cheng, J. H., and Major, E. O. (2004). JC virus induces nonapoptotic cell death of human central nervous system progenitor cell-derived astrocytes. *J Virol 78*, 4884-4891.

Seth, P., and Koul, N. (2008). Astrocyte, the star avatar: redefined. *J Biosci* 33, 405-421.

Sidoryk-Wegrzynowicz, M., Wegrzynowicz, M., Lee, E., Bowman, A.B., and Aschner, M. (2011). Role of astrocytes in brain function and disease. *Toxicol Pathol* 39, 115-123.

So, E. Y., and Kim, B. S. (2009). Theiler's virus infection induces TLR3-dependent upregulation of TLR2 critical for proinflammatory cytokine production. *Glia* 57, 1216-1226.

Sofroniew, M. V. (2009). Molecular dissection of reactive astrogliosis and glial scar formation. *Trends Neurosci* 32, 638-647.

Sofroniew, M. V., and Vinters, H. V. (2010). Astrocytes: biology and pathology. *Acta Neuropathol* 119, 7-35.

Suh, H. S., Brosnan, C. F., and Lee, S. C. (2009). Toll-like receptors in CNS viral infections. *Curr Top Microbiol Immunol* 336, 63-81.

Suzumura, A., Lavi, E., Weiss, S. R., and Silberberg, D. H. (1986). Coronavirus infection induces H-2 antigen expression on oligodendrocytes and astrocytes. *Science* 232, 991-993.

Szymocha, R., Akaoka, H., Dutuit, M., Malcus, C., Didier-Bazes, M., Belin, M. F., and Giraudon, P. (2000). Human T-cell lymphotropic virus type 1-infected T lymphocytes impair catabolism and uptake of glutamate by astrocytes via Tax-1 and tumor necrosis factor alpha. *J Virol* 74, 6433-6441.

Tan, L., Gordon, K. B., Mueller, J. P., Matis, L. A., and Miller, S. D. (1998). Presentation of proteolipid protein epitopes and B7-1-dependent activation of encephalitogenic T cells by IFN-gamma-activated SJL/J astrocytes. *J Immunol* 160, 4271-4279.

Titeux, M., Galou, M., Gomes, F. C., Dormont, D., Neto, V.M., and Paulin, D. (2002). Differences in the activation of the GFAP gene promoter by prion and viral infections. *Brain Res Mol Brain Res* 109, 119-127.

Toft-Hansen, H., Fuchtbauer, L., and Owens, T. (2011). Inhibition of reactive astrocytosis in established experimental autoimmune encephalomyelitis favors infiltration by myeloid cells over T cells and enhances severity of disease. *Glia* 59, 166-176.

van den Pol, A. N. (2009). Viral infection leading to brain dysfunction: more prevalent than appreciated? *Neuron* 64, 17-20.

Vass, K., and Lassmann, H. (1990). Intrathecal application of interferon gamma. Progressive appearance of MHC antigens within the rat nervous system. *Am J Pathol* 137, 789-800.

Verma, S., Kumar, M., and Nerurkar, V.R. (2011). Cyclooxygenase-2 inhibitor blocks the production of West Nile virus-induced neuroinflammatory markers in astrocytes. *J Gen Virol* 92, 507-515.

Wang, Z., Trillo-Pazos, G., Kim, S. Y., Canki, M., Morgello, S., Sharer, L. R., Gelbard, H. A., Su, Z. Z., Kang, D. C., Brooks, A. I., et al. (2004). Effects of human immunodeficiency virus type 1 on astrocyte gene expression and function: potential role in neuropathogenesis. *J Neurovirol* 10 *Suppl 1*, 25-32.

Westenbroek, R. E., Bausch, S. B., Lin, R. C., Franck, J. E., Noebels, J. L., and Catterall, W. A. (1998). Upregulation of L-type Ca^{2+} channels in reactive astrocytes after brain injury, hypomyelination, and ischemia. *J Neurosci* 18, 2321-2334.

Windhagen, A., Newcombe, J., Dangond, F., Strand, C., Woodroofe, M. N., Cuzner, M. L., and Hafler, D. A. (1995). Expression of costimulatory molecules B7-1 (CD80), B7-2 (CD86), and interleukin 12 cytokine in multiple sclerosis lesions. *J Exp Med* 182, 1985-1996.

Wyss-Fluehmann, G., Zurbriggen, A., Vandevelde, M., and Plattet, P. (2010). Canine distemper virus persistence in demyelinating encephalitis by swift intracellular cell-to-cell spread in astrocytes is controlled by the viral attachment protein. *Acta Neuropathol* 119, 617-630.

Yeh, T. H., Lee da, Y., Gianino, S. M., and Gutmann, D. H. (2009). Microarray analyses reveal regional astrocyte heterogeneity with implications for neurofibromatosis type 1 (NF1)-regulated glial proliferation. *Glia 57*, 1239-1249.

Yong, V. W. (1996). Cytokines, astrogliosis, and neurotrophism following CNS trauma. In *Cytokines and the CNS*, J. Ransohof, and E.N. Benveniste, eds. (Boca Raton, CRC), pp. 309-327.

Yong, V. W. (2002). Differential mechanisms of action of interferon-beta and glatiramer aetate in MS. *Neurology* 59, 802-808.

Zhang, D., Hu, X., Qian, L., O'Callaghan, J. P., and Hong, J. S. (2010). Astrogliosis in CNS pathologies: is there a role for microglia? *Mol Neurobiol* 41, 232-241.

Zheng, L., Calenoff, M. A., and Dal Canto, M. C. (2001). Astrocytes, not microglia, are the main cells responsible for viral persistence in Theiler's murine encephalomyelitis virus infection leading to demyelination. *J Neuroimmunol* 118, 256-267.