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Herpes Simplex Type I (HSV-1) Infection of the Nervous System: Is an Immune Response a Good Thing?

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Abstract

Herpes simplex virus type 1 (HSV-1) can induce a robust immune response initially thru the activation of pattern recognition receptors and subsequent type I interferon production that then shapes, along with other innate immune components, the adaptive immune response to the insult. While this response is necessary to quell virus replication, drive the pathogen into a “latent” state, and likely hinder viral reactivation, collateral damage can ensue with demonstrable cell death and foci of tissue pathology in the central nervous system (CNS) as a result of the release of inflammatory mediators including reactive oxygen species. Although rare, HSV-1 is the leading cause of frank sporadic encephalitis that, if left untreated, can result in death. A greater understanding of the contribution of resident glial cells and infiltrating leukocytes within the CNS in response to HSV-1 invasion is necessary to identify candidate molecules as targets for therapeutic intervention to reduce unwarranted inflammation coinciding with maintenance of the anti-viral state.

Keywords

Interferons; CNS; HSV-1; Encephalitis

1. Introduction to Herpes Simplex Virus-1

HSV-1 is a double-stranded DNA virus with a genome size of 152 kb encoding for at least 84 different polypeptides (McGeoch et al., 1988). During an *in vitro* acute infection, the lytic nature of the virus is driven by a sequential cascade of genes (referred to as lytic genes) expressed collectively over the course of the first 8-12 hours following entry into the host cell and includes the immediate early or α genes, early or β genes, and late or γ genes (Honess and Roizman, 1974). It is now appreciated that many of these genes encode proteins that serve dual functions: assist in the replication of virus and counter the innate or adaptive immune response

to the pathogen. Ultimately, the success rate of the virus within the human host is dependent upon its ability to establish a latent infection and then reactivate at opportune times and shed into bodily secretions that are passed vertically or horizontally to a naive patient.

2. Herpes Spread Into the CNS

HSV-1 gains entry into cells by binding to heparan sulfate proteoglycan and invading the host cell (neurons) during primary infection (Shieh et al., 1992; WuDunn and Spear, 1989). It has been shown that this first step of adsorption and infection are severely impaired when enzymatic digestion of cell surface heparan sulfate is performed, yet unaffected with digestion of dermatan sulfate or chondroitin sulfate (WuDunn and Spear, 1989). When comparing mutant cells lacking heparan sulfate to wild types cells, binding is also impaired, (Shieh et al., 1992; Shieh and Spear, 1994) suggesting the likelihood of heparan sulfate being an initial receptor of HSV-1. Experimental evidence shows HSV-1 glycoprotein (g) C and gB are vital components for viral attachment to the host cell (Reske et al., 2007). Without heparan sulfate, the ability of the virus to attach and infect the host cell is severely impaired.

While the virus can infect cells with the loss of either glycoprotein, a loss of both gC and gB renders the virion noninfectious. It has also been shown gB binds to specific cell surface receptors and directly fuses with the cell membrane or enters through fusion within an endosome in a low pH-dependent or a pH-independent environment (Nicola et al., 2003; Nicola et al., 2005). Thus, gB is involved in attachment and fusion to many host cell types in some fashion and coordinates infection in a multitude of cell types including neurons. Following attachment and fusion, the virus then uses gD interaction with herpesvirus entry mediator, nectin-1, or 3-O-sulfated heparan sulfate for viral entry (Reske et al., 2007). However, the exact process and all viral and cellular components involved in attachment and fusion are still unclear. In the case of neurons, once the virus has entered in an *in vivo* model of infection, it will then travel via axonal retrograde transport to infect the cell nucleus of sensory ganglia such as the trigeminal ganglion within the first 24 hours following infection (Shimeld et al., 2001). The rapidity of the virus traveling to the neuronal body of the sensory ganglia all but assures escape from the adaptive immune response such that the host's innate immune response is the primary arm of the immune system left to block HSV-1 replication and spread to the CNS. A significant portion of innate resistance lies with the type I interferon (IFN) response. Consequently, it should come as no surprise HSV-1 has a number of gene-encoded proteins that specifically target the type I IFN pathway including infected cell protein (ICP) 34.5, ICP0, and ICP27.

During primary infection HSV-1 replicates and thwarts viral-encoded protein translational arrest using ICP34.5 and ICP27 to inhibit activated protein kinase R and Jak/STAT signaling respectively in response to a vigorous immune response (Leib et al., 2000; Mossman and Smiley, 2002; Johnson et al., 2008). The virus circumvents host cell defense using ICP0 and virion host shutoff (vhs) antagonism of Stat I and thus IFN production (Yokota et al, 2001; Chee and Roizman, 2003; Halford et al., 2006; Pasieka et al., 2008; Harle et al., 2002). ICP0 accomplishes this process by inhibiting activation and nuclear accumulation of interferon regulatory factor (IRF)-3 and IRF-7 mediated by the ICPO RING finger domain (Lin et al., 2004; Melroe et al., 2004). In addition, ICP0 disperses nuclear domain-10 nuclear bodies that are normally associated with transcription regulation, growth suppression, and apoptosis (Maul et al., 1993; Everett and Zafiropoulos, 2004). Contrary to previous studies (Steiner et al., 1990; Sears et al., 1991; Ecob-Prince et al., 1993), a recent *in vivo* investigation has reported that virus lacking an early transcribed viral particle-16 (VP16), which mediates transcription of immediate early genes, does not exit latency (Thompson et al., 2009). In addition, it has also been reported ICP0 deficient HSV-1 maintains similar viral protein levels as the parental wild type counterparts in cell culture (Thompson et al., 2009) and are still able to reactivate (Preston, 2007). Taken together, these studies suggest VP16 could play a role in mediating transcription

of early viral particles but also rely on ICP0-mediated interference of host anti-viral defenses to fully reactivate. Whether these coordinated events allow the virus to exit latency and reactivate still remains unproven. The impact of ICP0 expression in the CNS is not fully understood although ICP0 mutants do not replicate to the same extent as parental virus unless the type I IFN pathway is compromised (Halford et al., 2006). Conversely, over expression of type I IFNs in the CNS is found to enhance resistance to HSV-1 infection (Carr et al., 1998). Therefore, it would appear to be a race between type I IFN activation of antiviral pathways and HSV-encoded proteins to counter the effects of the IFN pathway and the adaptive immune response that ultimately dictates whether the virus will prevail and establish a latent infection.

After the acute infection, the virus establishes latency in A5+ and KH10+ sensory ganglion cells (Bertke et al., 2009) and is thought to remain dormant until reactivation. Experimentally though, HSV-1 causes localized incomplete or low level lytic infection (Feldman et al., 2002) causing a persistent immune response during latency (Cantin et al., 1995; Shimeld et al., 1995; Halford et al., 1996; Liu et al., 1996). Daily exposure to the antiviral drug acyclovir significantly reduces the localized immune response within the ganglion during latency (Halford et al., 1997). Thus, the virus continuously undergoes incomplete or low level reactivation until such circumstances allow it to fully reactivate and perpetuate spread to naive recipients.

3. Host Cell Response to HSV-1 Infection: The Toll-like receptor (TLR)

The lytic cycle of HSV-1 evokes an intricate immunological response in the CNS. One of the earliest steps in the immune process is the binding of viral invariant structures known as pathogen-associated molecular patterns (PAMPs) to toll-like receptors (TLRs), a type of pattern recognition receptor (PRR), to initiate the innate immune response and inflammation (Medzhitov and Janeway, 2002). TLRs are single membrane spanning receptors with extracellular leucine-rich repeats and an intracellular signaling Toll/IL-1 receptor domain [TIR] (Takeda et al., 2003) found on cell membranes and cell compartments that recognize specific molecular patterns. Once they bind foreign molecules like HSV-1 proteins or viral nucleic acid, they activate the innate immune response by dimerizing and inducing the production of chemokines, proinflammatory cytokines, and up-regulation of cell surface receptors through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), or a p38 mitogen-activated protein kinase (MAPK) and c-Jun NH_2-terminal kinase (Jnk) activation of AP-1 (Akira et al., 2001; Karin, 1995). These molecules drive inflammation and prime the host adaptive immune response through further signaling pathways (Fig. 1). One critical anti-viral group of molecules elicited by 5 of the 10 human TLRs and 4 of the 12 mouse TLRs are the type I IFNs (Zhang et al., 2007a).

Several TLRs have been implicated as important mediators of viral containment and/or destructive inflammation in response to HSV-1 infection of the CNS. Specifically, one of the most important TLRs to mediate host cell response to HSV-1 is TLR-2, which is found on the cell surface of microglia and astrocytes in the CNS (Kielian, 2006). TLR-2 signals through a myeloid differentiation factor 88 (MyD88) or toll-interleukin 1 receptor domain containing adaptor protein (TIRAP)-dependent cascade to activate downstream DNA binding proteins like NF-κB to increase transcription of various interleukins (IL) and tissue necrosis factor (TNF) (Yamamoto et al., 2002; Akira and Takeda, 2004; Akira et al., 2006; O'Neill and Bowie 2007). It has been reported TLR-2 deficient mice have a blunted cytokine and chemokine (monocyte chemoattractant protein1) response to lethal HSV-1 infection, yet a reduction in mortality, inflammatory brain lesions, partial or total paralysis, and/or seizures (Kurt-Jones et al., 2004). Another group has reported TLR-2 acts in concert with TLR-9 to control HSV-1 and HSV-2 infection through NK cell recruitment in the brain to decrease viral loads (Sato et al., 2006; Sorensen et al., 2008). How such observations can be reconciled is currently

unknown. Identifying the role of various TLRs and downstream pathways activated in the CNS in response to HSV-1 continues to be an actively studied area.

Another aspect of the immune response regulated by TLR-2 is the induction of the IL-15 gene in response to HSV-1 (Ahmad et al., 2008). IL-15 with IL-21 elicits proliferation of naive and memory $CD8^+$ T cells (Rodrigues et al., 2009) that likely monitor and control virus replication and spread. One detrimental outcome from $CD8^+$ T cell activation is the targeted destruction of virally-infected cells which could have significant consequences as a contributor to neuropathology dependent upon the viral load within the CNS (Lellouch-Tubiana et al., 2000; Anglen et al., 2003).

TLR-3 is found in cell compartments of microglia, astrocytes, oligodendrocytes, and neurons (Bsibsi et al., 2002; Olson and Miller, 2004; Carpentier et al., 2005; Farina et al., 2005; Prehaud et al., 2005; Scumpia et al., 2005). It has been shown to prime the immune system in response to double-stranded HSV-1, non-transcribed RNA intermediates during infection through a MYD88-independent pathway resulting in the activation of NF-κB and IRF-3 (Alexopoulou et al., 2001; Doyle et al., 2002; Akira and Takeda, 2004; Takeda and Akira, 2004; Boehme and Compton, 2004; Akira et al., 2006; O'Neill and Bowie 2007; Onoguchi et al., 2007). While NF-κB is activated by other TLRs in response to HSV-1, IRF-3 is mobilized solely by TLR-3 or -4 and induces a specific set of genes necessary for viral defense (Doyle et al., 2002). In individuals lacking TLR-3 and thus IRF-3 activation, an impaired IFN-dependent containment of the virus has been reported (Casrouge et al., 2006). The susceptibility is likely due to a decreased ability to signal through TIR-domain-containing adaptor-inducing IFN-β (TRIF), a binding protein that interacts with TLR-3 (Sato et al., 2000; Yamamato et al., 2003; Town et al., 2006; Zhang et al., 2007b). Thus, cells are unable to activate antiviral effector molecules including RNAse L and double-stranded RNA-dependent protein kinase (PKR) to inhibit viral spread and can succumb to encephalitis like that reported in West Nile Virus meningoencephalitis (Samuel et al, 2006). TLR-3 activation in neuronal cells is associated with increased resistance to HSV-1 infection and an increase in the production and heightened response to IFNs (Prehaud et al., 2005; Delhaye et al., 2006; Boivin et al., 2008; Zhou et al., 2009). Such observations reinforce the central role of type I IFNs as necessary components to contain virus within the CNS (Delhaye et al., 2006).

TLR-9, a PRR that recognizes unmethylated CpG DNA, (Akira and Hemmi, 2003; Takeda et al., 2003; Hemmi et al., 2003) is found in endosomes/vacuolar compartments of microglia and astrocytes (Dalpke et al., 2002; Bsibsi, et al., 2002; Bowman et al., 2003; Olson et al., 2004; Jack et al., 2005). It mediates an early and rapid production of type I IFNs through an IRAK-4 and MYD88-dependent pathway in response to HSV-1 (Krug et al., 2004; Kawai et al., 2004; Yang et al., 2005; Rasmussen et al., 2007). Recently, TLR-9 has been found to operate through the PI(3)K-mTOR-p70S6K pathway in plasmacytoid dendritic cells to induce type I IFNs (Cao et al., 2008). TLR-9 has also been implicated in influencing hematopoiesis towards production of plasmacytoid and IFN producing killer dendritic cells at the expense of lymphoid precursors (especially B lymphocytes) (Welner et al., 2008). This becomes relevant in viral infections that activate TLR-9 since plasmacytoid dendritic cells can secrete large amounts of IFNs once mature and thus become a vital link between host innate and adaptive immune systems (Biron, 2001; Dai et al., 2004; Kadowaki et al., 2000).

4. The Interferon Response to HSV-1 in the CNS

Binding of viral particles and activation of PRRs, such as mannose receptors, TLRs, and cytosolic receptors induce type I IFN production through MYD88-dependent and -independent pathways (Malmgaard, 2004; Malmgaard et al., 2004). Type I IFNs are secreted by infected cells and work in an autocrine or paracrine manner to induce resistance to viral spread. They

play a vital role in the host cell response signaling through the Jak-Stat pathway (Darnell et al., 1994; Aaronson and Horvath, 2002; Malmgaard, 2004) and induce expression of RNAse L, PKR, and Mx protein GTPases (Zhou et al., 1993; Samuel, 2001). RNAse L acts to degrade all intracellular mRNA (cellular and foreign), while PKR causes translation cessation. These two processes drastically reduce viral replication in the cell and are used by the cell to inhibit viral proliferation. In addition to these anti-viral properties, PKR and RNAse L are mediators of cell death through apoptosis (Zhou et al., 1997; Barber, 2005).

IFNs also augment maturation of dendritic cells and activate NK cells, dendritic cells, B and T lymphocytes (Mossman and Ashkar, 2005) and maintain and facilitate clonal expansion of activated T cells (von Hoegen, 1995; Marrack et al., 1999; Kolumam et al., 2005). IFN-α enhances TLR responsiveness by up-regulating TLR-3, -4, and -7 (Siren et al., 2005; Tissari et al., 2005) priming these cells to produce massive quantities of IFNs and cytokines (Garcia-Sastre and Biron, 2006). If such production arises in organized lymphoid tissue, the paracrine signaling acts to promote clonal expansion of cytotoxic T cell precursors (Curtsinger et al., 2005).

Experimentally in the absence of the type I IFN receptor (IFNAR), mice succumb to systemic HSV-1 dissemination (Luker et al., 2003) with two- to three-fold increased levels of circulating monocytes and neutrophils (Muller et al., 1994). The leukocytosis is likely due in part to TLR-9 driven myeloid cell differentiation (Welner et al., 2008). In the absence of the principal subunit of the type I IFN receptor IFNAR-A1 ($CD118^{-/-}$), the increased sensitivity to HSV-1 infection is reflected by a loss of draining mandibular lymph node integrity. There is a massive loss of T and NK cells as well as macrophages in the lymph nodes (Conrady et al., 2009) evident by the pronounced loss of primary and secondary follicles by day 5 post infection (Fig. 2). As a result, the generation of HSV-specific cytotoxic T cells is dramatically reduced which likely contributes to poor viral surveillance in the peripheral and central nervous systems resulting in rapid death (Fig. 3) (Conrady et al., 2009).

Although T cell numbers are reduced within the nervous system of the $CD118^{-/-}$ mice, macrophage numbers are elevated (Conrady et al., 2009). The effect of increased macrophage trafficking to the CNS has not been firmly established. However, one group has found depletion of neutrophils or macrophages during HSV-1 infection increases mouse survival (Lundberg et al., 2008). The authors conclude the inflammatory response and increased mortality is due to a failure to control inflammation rather than HSV-1 destruction of the CNS. While the study seems to implicate macrophage and neutrophil-dependent CNS devastation in response to HSV-1 infection, further studies are required to eliminate the contribution of additional leukocyte populations in the neuropathology.

In addition to the risk of disseminated disease, the lack of IFNs or a pathway intermediate in the production of IFNs can have drastic consequences as well. For example, an autosomal recessive deficiency in UNC-93B (an endosomal protein important in TLR-3, TLR-7, and TLR-9 signaling) found in some children is found to increase susceptibility to herpes encephalitis due to a deficiency in IFN-α/β production through TLR-3 signaling, yet these children have a typical immune response to other viral encounters (cytomegalovirus, varicella zoster virus, Epstein-Barr virus, parvovirus B19, respiratory syncitial virus, parainfluenza-1, influenza A and B, human herpes virus-6, and immunized with live measles/mumps/rubella and poliovirus vaccines) (Casrouge et al., 2006). Thus, UNC-93B-dependent production of IFNs is necessary for host defenses against CNS HSV infection, yet seems to be redundant for effective immune responses to other pathogens.

Clearly, the inability to generate a robust adaptive immune response due to aberrant innate immune activation will ultimately lead to a loss in viral containment and spread from the

peripheral nervous system to various areas of the brain. The toxic metabolites of large numbers of activated microglia including nitrous oxide could cause widespread damage (Marques et al., 2008) and thus severe CNS pathology. Therefore, the question arises: is it the loss of viral containment within the periphery resulting in a large viral burden in the CNS which then elicits resident cell (astrocyte and microglia) activation and production of toxic metabolites that ultimately harms the host, the recruitment of activated leukocytes (e.g., macrophages, $CD4^+$ and $CD8^+$ T cells) that release cytolytic molecules resulting in massive cell death of infected neurons, astrocytes, and oligodendrocytes, or the combination of these events that contributes to significant neuropathology including encephalitis? Ironically, one report suggests microglia, unlike astrocytes, harbor HSV-1 without overt cytopathic effect and therefore, may act as a reservoir for persistent low level release of virus and cytokines that over a long period of time may have detrimental consequences to the host (Baker et al., 1999).

5. Clinical Course: the human significance

HSV-1 is a highly successful human pathogen. This is shown by seroprevalance studies demonstrating widespread transmission in childhood such that 39% of individuals 14-19 years of age are already infected, and prevalence rates increase to 65.3% by middle adulthood (Xu et al., 2006). The vast majority of transmission in the general population is through saliva and less commonly through genital transmission, and infection is usually asymptomatic or manifest as a simple “cold sore” on the labia with little further sequelae. Nevertheless, a small fraction of patients HSV-1 infection develop more serious diseases of the CNS, the most notable of which is encephalitis. The yearly incidence of HSV-1 encephalitis has been estimated at 2-4 cases /1,000,000 individuals (Hjalmarrson et al., 2007; Skoldenberg et al., 1984; Whitley, 2006). It is also the most common cause of sporadic viral encephalitis and was responsible for 75% of hospitalizations for viral encephalitis in the United States prior to the introduction of West Nile Virus to North America (Khetsuriani et al., 2002).

HSV-1 encephalitis occurs in all age groups and has been described as having a bi-modal distribution although the majority of cases are in adults over the age of 50 (Hjalmarrson et al., 2007; Whitley, 1990.). Earlier reports suggested that it was not more common in immunosuppressed patients; however, more recent studies identified children specific mutations in UNC-93B and in TLR3 that impair host defenses against HSV (Zhang et al., 2008). By comparison, individuals with IFNγ-R-deficiency, STAT 1 deficiency, or pharmacological immunosuppression such as by anti-TNF-α monoclonal antibody are also at risk for HSV encephalitis as well as a variety of other viral and bacterial infections (Dupuis et al., 2003; Dorman et al., 1999; Bradford et. al., 2009.).

More than 80% of patients with HSV-1 encephalitis present with the triad of fever, headache, and altered level of consciousness and 97% of patients with biopsy proven HSV infection have CSF pleocytosis (Whitley et al., 1982). Other less common presentations are also possible such as a symmetrical brainstem inflammatory course with lesions associated with vasogenic edema (Miura et al., 2009). In addition, the presentation in neonates and young children differs from that of adults by being more frequently diffuse and or multi-focal (Kleinschmidt-DeMasters and Gilden, 2001; Batnitzky et al., 1986). These different presentations may reflect different mechanisms of CNS invasion between adults on the one hand and neonates / young children on the other. For example, recent data show that 34% of 32 children aged 9-44 months with primary HSV-1 gingivostomatitis were viremic by polymerase chain reaction (PCR) (Harel et al., 2004.). Although viremia can also be demonstrated in adults, it is possible that immaturity of the blood-brain barrier and the immune system in young children allow the virus to seed the CNS in a fashion not found in adults which lends itself to multi-focal or atypical disease in the setting of reactivation. Signs of temporal lobe involvement, e.g. personality changes, are suggestive of HSV encephalitis history, but clinical features and routine CSF parameters

(protein concentration, leukocyte count, erythrocyte count) alone are not sufficient to distinguish CNS infection caused by HSV from encephalitis caused by other pathogens or to exclude it from further consideration (Whitley et al., 1982; Whitley et al., 1989). Definitive diagnosis requires demonstration of virus in the cerebral spinal fluid (CSF) or brain tissue by culture or histology, but it is most commonly accomplished by PCR methodology of CSF (Cinque et al., 1996.) Use of PCR containing multiple species-specific primer pairs has the advantage of distinguishing HSV-1 from other neurotropic herpesviruses such as HSV-2 and varicella zoster virus (VZV), as well as identifying mild or atypical cases of HSV-1 infection (Ihekwaba et al., 2008; Fodor et al., 1998). Gadolinium-enhanced magnetic resonance imaging is the optimal choice for neuroimaging and electroencephalography can reveal a characteristic temporal focus of periodic lateralized epileptiform discharges that suggests a diagnosis of HSV encephalitis (Steiner et al., 2005). On a histological level most cases in adults show a characteristic necrotizing, hemorrhagic encephalitis that is usually in a frontal-temporal distribution (Kleinschmidt-DeMasters and Gilden, 2001).

Before effective antiviral agents were available, HSV encephalitis had a mortality rate widely quoted at 70% and permanent neurological deficits afflicted many, if not most, of the survivors (Whitley et al., 1977). The superiority of acyclovir over vidarabine was established by 2 landmark clinical trials over 20 years ago and acyclovir remains the drug of choice for treatment for most patients today (Sköldenberg et al., 1984; Whitley et al., 1986). The main exception to this is individuals infected with acyclovir resistant virus. This is quite uncommon (< 1%) in the general population, but can be problematic in immunosuppressed patients reaching levels as high as 30% in some bone marrow transplant patients (Kimberlin, 2007). In such cases treatment options include cidofovir and foscarnet, drugs that are more toxic than acyclovir yet retain activity against acyclovir-resistant virus (Losada et al., 2002; Superti et. al., 2008). Nonetheless, even with treatment these studies and others report mortality rates of 14%-28% and severe neurological disabilities in an additional 9%-33% with a high prevalence of seizures (Raschilas et al., 2002; McGrath et al., 1997; Hjalmarrson et al., 2007.). In contrast only 38% to 65% of affected individuals have a good outcome, i.e. return to pre-infection level of functioning.

This unsatisfactory prognosis begs the question of the extent to which modulators of the immune response, e.g. glucocorticoids, could improve outcomes in HSV encephalitis as they have been shown to do in some forms of bacterial meningitis. However, unlike the situation with bacterial meningitis, there are no randomized, placebo-controlled trials demonstrating the effectiveness of corticosteroids in humans with HSV encephalitis on which to base strong recommendations (Steiner et al., 2005, Tunkel et al., 2008, Fitch and van de Beek, 2008). Nevertheless, experimental rodent models of HSV encephalitis and anecdotal experience in humans may be instructive. For example, studies using dexamethasone alone beginning 3 days after intranasal infection of mice showed reduced viral replication and prolonged survival compared with no treatment (Sergerie et al., 2007). In a different study, mice treated with acyclovir plus methylprednisolone resulted in a significant reduction of the severity of long-term MRI abnormalities and no increase in viral replication compared with acyclovir treatment alone (Meyding-Lamade et al., 2003). In addition, there are case reports in adult and pediatric clinical medicine also suggest that high doses of corticosteroids are not harmful, and can be helpful in selected patients such as those with severe brain edema (Nakano et al., 2003; Musallam et al., 2007). Furthemore, a retrospective analysis of 45 patients treated for HSV encephalitis, some of whom received dexamethasone, found that receiving this drug in addition to acyclovir was an independent predictor of a good outcome (Kamei et al., 2005). These data and others provided a rationale for a multicenter, randomized, placebo-controlled trial known as the GACHE trial (German trial of Acyclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis) designed to answer the question of whether dexamethasone should be used along with acyclovir as adjunctive therapy to diminish collateral damage that ensues as a result of

infection and the immune response to it (Martinez-Torres et al., 2008). Until systematic clinical studies like the GACHE trial show the efficacy of steroid therapy as well as the optimal protocol for their dosage and administration, the use of adjunctive corticosteroids remains an option for adjunctive therapy in patients with HSV encephalitis and severe brain edema or vasculitis left to the judgment of the attending physician (Fitch and van de Beek, 2008).

6. Potential long-term consequences of HSV-1

HSV-1 infection of the CNS can have lifelong effects such as permanent temporal lobe damage. Recent reports have surfaced that link Alzheimer's disease and HSV-1 (Dobson and Itzhaki et al., 1999; Itzhaki and Wozniak, 2008) consistent with an earlier report (Middleton et al., 1980). HSV-1 has been shown to phosphorylate microtubule-associated tau, the main component of neurofibrillary tangles found in Alzheimer's disease, at several sites including serine 202, threonine 212, serine 214, serine 396, and serine 404 (Wozniak et al., 2009). The virus has also been shown to lead to dramatic increases in the intracellular levels of β-amyloid proteins, the major protein found in senile plaques of Alzheimer's disease in neuronal and glial cell cultures (Wozniak et al., 2007). These neurofibrillary tangles and senile plaques in the CNS are pathopnuemonic for a diagnosis of Alzheimer's disease in the elderly with dementia. If indeed HSV-1 is proven to be one of several neurotropic pathogens that contribute to CNS disease including Alzheimer's, alternative treatment options including vaccines (Lin et al., 2001) may limit the long-term consequences of CNS destruction.

7. Conclusion

While many studies are beginning to implicate the immune response to HSV-1 and its various cell populations (e.g. microglia, $CD8^+$ T cells) in causing widespread CNS pathology (Fischer and Riechman, 2001; Anglen et al., 2003; Bien and Bauer, 2005; Skoldenberg et al., 2006; Sobel et al., 1986; Marques et al., 2008), the exact cause of the extensive destruction of the CNS is still unclear. The issue arises that only a few studies have incorporated human subjects or even animal models to study the response to HSV-1 making it difficult to apply to clinical medicine. The complex interaction between the immune response and the virus cannot be distilled down *in vitro* using cell lines and targeted mutations of select HSV-1 genes as this would exclude the host adaptive immune response, a major component involved in the maintenance of viral latency (Knickelbein et al., 2009) and tissue damage associated with much of the morbidity in the human host. Thus, emphasis should be placed on *in vivo* models including cases of human genetic anomalies (Casrouge et al., 2006) in order to attain a better understanding of components that contribute to CNS pathology in response to HSV-1.

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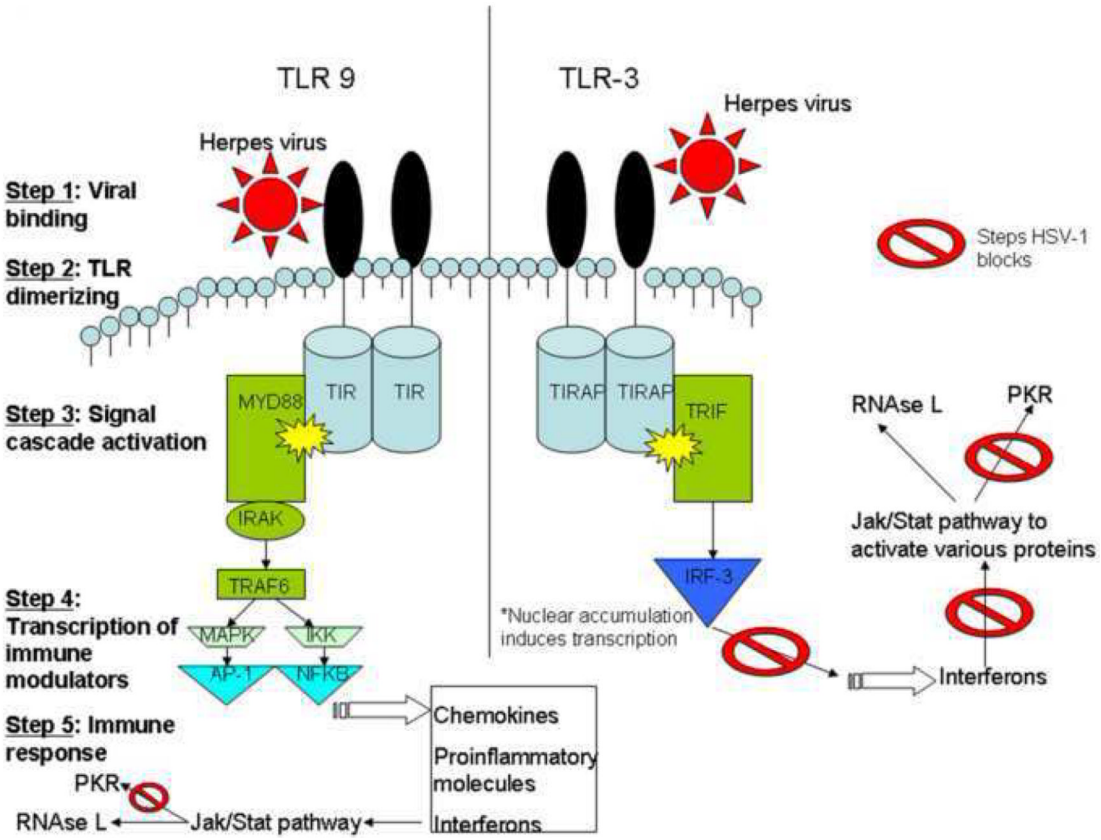

Figure 1.

Mechanisms of HSV-1-mediated antagonism of TLR-dependent, anti-viral pathways. TLR-3 signals in a MYD88-independent manner to induce interferon production, while TLR-9 activates inflammatory cytokines and interferons through a MYD88-dependent pathway in response to HSV-1 infection. HSV-1 blocks ND10 accumulation in the nucleus, PKR activity, and Jak/STAT signaling with a cumulative effect that renders the infected cell highly susceptible to viral replication.

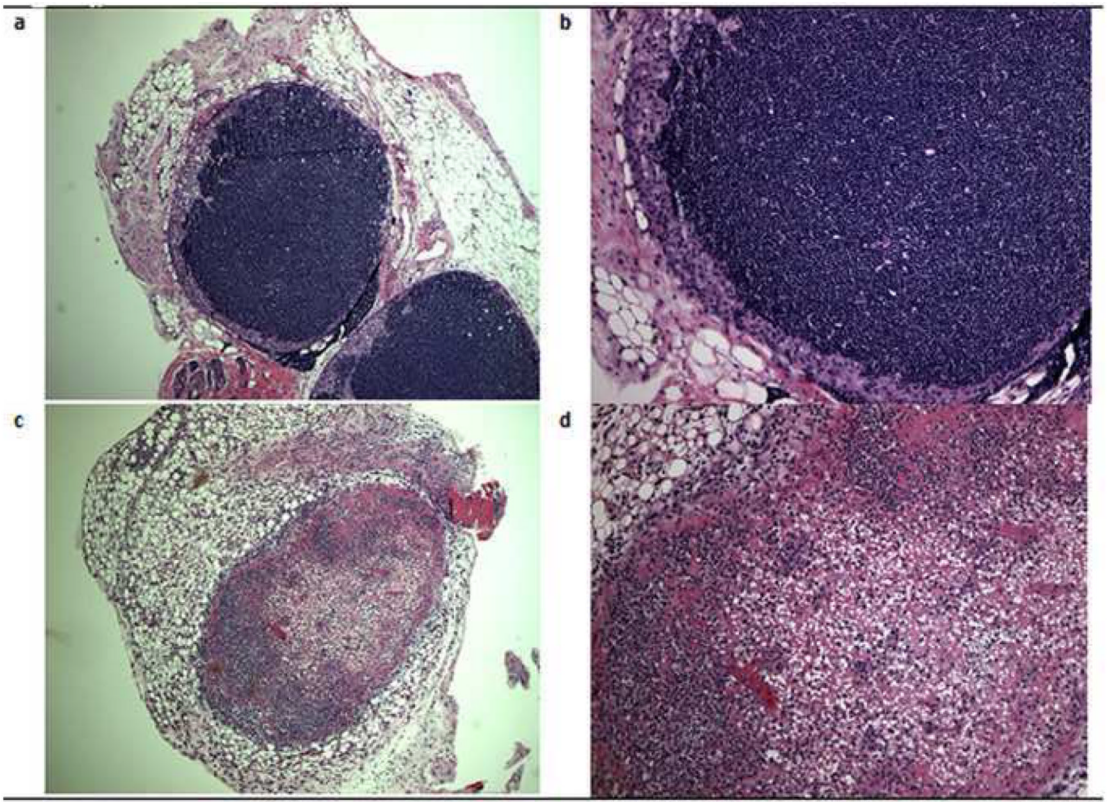

Figure 2.

The absence of a functional type I IFN receptor results in a massive loss of cells populating the draining (mandibular) lymph node following ocular HSV-1 infection. Wild type and IFNRA1 deficient mice (CD118-/-) were infected with 1,000 plaque forming units of HSV-1 (McKrae strain) in the cornea. Five days post infection, the mice were exsanguinated and the mandibular lymph nodes were removed, sectioned, and H&E stained. The results are representative of three experiments, two mice/group/experiment. (**a**) Wild type mouse lymph node showing normal lymph node integrity at 40x magnification and (**b**) 100x magnification. (**c**) Lymph node from a $CD118^{-/-}$ mouse with widespread cell death resulting in a loss of cells at 40x magnification, and (**d**) 100x magnification.

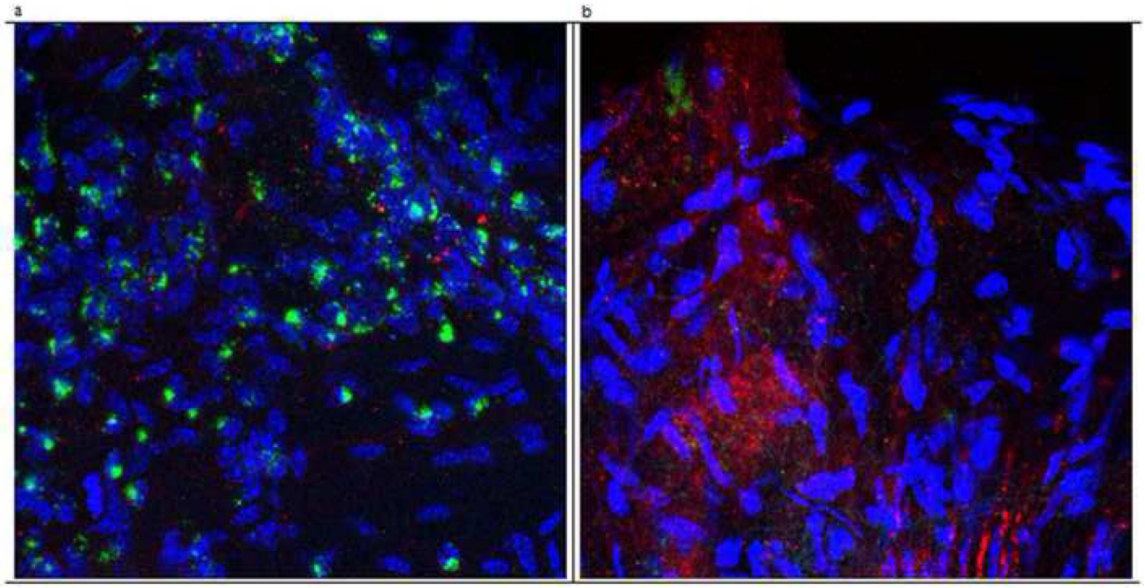

Figure 3.

Type I IFN receptor deficient mice show increased expression of HSV-1 antigen and reduced $CD3^+$ T cell infiltration in the trigeminal ganglia following ocular infection with HSV-1. Wild type and IFNRA1 deficient mice (CD118-/-) were infected with 1,000 plaque forming units of HSV-1 (McKrae strain) in the cornea. Five days post infection, the mice were exsanguinated and the trigeminal ganglia were removed and processed for whole mount staining using polyclonal phycoerythrin-conjugated anti-HSV-1 (red) and fluorescein isothiocyanate-conjugated anti-CD3 (green) antibodies. (**a**) Trigeminal ganglion of a wild type mouse at 400x magnification showing T cell infiltration with little appreciable HSV-1 antigen expression. (**b**) Trigeminal ganglion from a $CD118^{-/-}$ mouse at magnification of 400x with a constellation of HSV-1 antigen expression but few T cells residing in the tissue. Nuclei were stained with DAPI (blue). This figure is representative of three trigeminal ganglia per group.