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The Immunopathogenesis of Neurotropic Flavivirus Infection

King NJC et al.
University of Sydney
Australia

1. Introduction

The flavivirus genus in the Flaviridae family comprises over 70 species, most of which are tick- or mosquito-borne. They are single-stranded, plus-sense RNA viruses, responsible for significant human and animal morbidity and mortality on all inhabited continents. Medically important viscerotropic flaviviruses include dengue, found equatorially across the world, and the prototypic yellow fever virus, found in Africa and South America. Neurotropic members include tick-borne encephalitis virus (TBEV) in Europe, West Nile virus (WNV) in Africa, parts of Europe and the Indian subcontinent, as well as the USA, St Louis encephalitis virus in the USA, and Japanese encephalitis (JEV) and Murray Valley encephalitis (MVE) viruses in Australasia. Many of these have a history of emergence and re-emergence; indeed, following a novel outbreak in 1999 in New York (Lanciotti et al., 1999; CDC, 2010), WNV spread virtually throughout the Americas in less than 10 years and is the most common cause of meningoencephalitis in North America. WNV is now perhaps the most widely spread of all flaviviruses and may comprise 4 or more lineages, based on isolate homologies (C.G. Hayes, 2001; Bakonyi et al., 2005; Vazquez et al., 2010), with Lineage I and II well-defined and of obvious clinical importance in animals and humans (E.B. Hayes et al., 2005; Venter et al., 2009). WNV was first isolated in 1937 in the West Nile region of Uganda (Smithburn et al., 1940). It is a member of the Japanese encephalitis serogroup, together with JEV, Murray Valley and Saint Louis encephalitis viruses (Poidinger et al., 1996). These viruses are usually propagated in a zoonotic cycle between mosquitoes and amplifying hosts, particularly birds (or pigs in the case of JEV), with humans being incidental, since they may not develop high enough virus titres to infect arthropod vectors (C.G. Hayes, 2001). Rare cases of human-to-human WNV transmission have been documented via organ transplants and blood transfusion, as well as vertical transmission to the foetus in utero (Iwamoto et al., 2003; Lindsey et al., 2009). Although less than one percent of WNV infections develop neuroinvasive disease, in some 60% of patients presenting with central nervous system (CNS) symptoms denoting neuroinvasive disease, life-threatening encephalitis supervenes (Samuel & Diamond, 2009). The young,
immunocompromised and elderly are at highest risk of developing encephalitis (Weiss et al., 2001; Guarner et al., 2004; Lindsey et al., 2009). Climate change, geographic factors and international travel, as well as local factors, such as mosquito rates and land clearing (E.A. Gould & Higgs, 2009) are cited as influencing the spread and prevalence of arbovirus infections across the globe. Despite considerable effort, the only successful live attenuated vaccine for neurotropic flaviviruses is for JEV (X. Liu et al., 2011), although considerable success has been achieved with a killed vaccine for TBEV (Barrett et al., 2003; Heinz et al., 2007). Treatment for all flavivirus encephalitides remains palliative. Indeed, one of the cardinal features of flavivirus infection complicating treatment approaches is immunopathology, evident in human cases and demonstrable in various animal models. In this review, we analyse the principal elements involved in the immunopathogenesis of flavivirus disease, with a view to novel constructive approaches to disease intervention.

2. Local flavivirus infection - responses of infected cells

Live WNV infection of various cell types leads to an upregulation of various cellular adhesion molecules, either directly or co-modulated by cytokines (Shen et al., 1995b; Shen et al., 1997; Arnold et al., 2004). These molecules include major histocompatibility complex (MHC) class I and II, intracellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1) and E-selectin (King & Kesson, 1988; Argall et al., 1991; Shen et al., 1997; Verma et al., 2009). The increase in MHC-I in mouse embryonic fibroblasts is independent of tumour necrosis factor (TNF) (Cheng et al., 2004b), although many cell types produce it in response to infection. In both mouse embryonic fibroblasts and human skin fibroblasts it can be induced by type I interferon (IFN)-dependent and -independent pathways (King & Kesson, 1988; Kesson & King, 2001; Cheng et al., 2004a), with the IFN-independent pathway relying on the activation of the transcription factor nuclear factor-κB (Kesson & King, 2001). This seemingly paradoxical increase in immune recognition molecule expression may enable evasion of early NK responses in vivo (Lobigs et al., 2003).

3. Earliest local changes in dermis and draining lymph nodes

Flaviviruses, transmitted by the bite of an infected mosquito, are injected with saliva during feeding. While several structural cell types are likely to come into contact with injected virus, the first leukocyte subset that virus is likely to encounter is the Langerhans cell (LC). LC are dendritic cells (DC) in the epidermis replenished by myeloid precursors in the bone marrow (BM) (Steinman, 1991; Merad et al., 2002). Following cutaneous inoculation, virus may infect LC, which increases cell surface expression of MHC-I, MHC-II, adhesion molecules, as well as costimulatory molecules, such as CD80, differentiating into a migratory phenotype in the process (Johnston et al., 1996). LC migrate to draining lymph nodes (DLN) in an accelerated manner in response to live virus, due to the induced soluble factor milieu (Johnston et al., 2000). In vivo experiments in mice show that the cytokine IL-1β is crucial for the emigration of LC from the epidermis to DLN (Byrne et al., 2001). It is presumed that these DC pass antigen to CD8α+ DC in the DLN, since LC alone evidently do not initiate antiviral immune responses (Allan et al., 2003; Kissenpfennig et al., 2005; Hildner et al., 2008), but direct evidence of WNV antigen transfer has yet to be shown. While mosquito saliva may skew adaptive responses towards a more Th2-like response profile.
(Schneider et al., 2007; Schneider et al., 2010), it is still unclear how its early presence influences disease outcome, since WNV infection in the genetic absence of IFN-γ still results in the generation of neutralising immunity (King et al., 2003). Arrival of virus in the DLN is accompanied by significant induction of CCL2 expression there that recruits monocyte-derived macrophages (MDM) from the bone marrow. The bone marrow undergoes a significant myeloid response to infection, releasing monocytes with a qualitatively different phenotype from the homeostatic state. Monocytes rapidly become TipDC (producing TNF and nitric oxide) in the DLN and likely contribute to the initiation of type 1 immune responses by inducing more IFN-γ from responding T cells than other DC subtypes in the DLN (Davison & King, 2011). Since flaviviruses significantly upregulate MHC expression on infected cells (King & Kesson, 1988; Shen et al., 1997), it is of interest how this influences the outcomes of innate immune interactions, such as with NK cells, and/or bears on the ultimate affinities of later adaptive cytotoxic T cell responses, reviewed in detail elsewhere (King & Kesson, 2003; Lobigs et al., 2003; King et al., 2009).

At the same time, at the dermal site of infection, CCL2, produced by infected cells, also recruits considerable numbers of MDM, which surround the infected focus, becoming DC within 24h of arrival. While it would appear that the DLN and dermis, by both producing CCL2, compete for MDM from the bone marrow, it seems likely that a subtly different cytokine milieu at each site selects for specific MDM subsets. This is suggested by adoptive transfer studies of flow cytometrically-sorted BM-derived monocyte subsets during infection. Thus, although similar numbers of inflammatory (Ly6C<sup>hi</sup>) monocytes migrated to each site, 5-fold more Ly6C<sup>lo</sup> monocytes migrated to the DLN than Ly6C<sup>hi</sup>, while some 2-fold more Ly6C<sup>hi</sup> monocytes migrated to the focus of infection in the skin than Ly6C<sup>lo</sup> monocytes. Perhaps consonant with these proportions, immigrant Ly6C<sup>lo</sup> monocytes in the DLN were 3-fold more likely to become DC, while in the dermis, immigrant Ly6C<sup>hi</sup> cells were 2-fold more likely to become DC. This suggests that other chemokines may differentially contribute to the recruitment of these cells to the relevant site, but more importantly, it suggests that relevant precursors to specific cells are already ordained before they reach their target site, rather than necessarily being randomly and non-specifically recruited (e.g., by CCL2) and induced to differentiate once they have arrived. Irrespective, it is evident that Ly6C expression on immigrating monocytes quickly changes at both sites, with downregulated Ly6C expression being the end point in both subsets. Thus, as shown in ours and other studies, Ly6C<sup>hi</sup> monocytes arriving in response to infection quickly downregulate expression of this molecule (Sunderkotter et al., 2004; Leon et al., 2007; Getts et al., 2008; Davison & King, 2011). In contrast, at both sites, within 24h, immigrating Ly6C<sup>lo</sup> monocytes become Ly6C<sup>hi</sup> at the site, only to downregulate expression of this molecule again within a further 24h, while also upregulating CD11c to become DC. Furthermore, in the dermis, it is exclusively these cells originally entering the dermis as Ly6C<sup>lo</sup> monocytes, that then migrate from the dermis to the DLN, presumably carrying viral antigen with them (Davison & King, 2011). Since so many Ly6C<sup>lo</sup> cells also migrate from the BM to the DLN to become DC, it is tempting to speculate that these cells may differentiate into the final migratory couriers of antigen between the subcapsular sinus of the DLN, where DC arrive from the dermis via the afferent lymphatics, to the CD8α<sup>+</sup> DC in the deep paracortex.

Early antiviral activity by Ly6C<sup>hi</sup> monocyte-derived TipDC in the dermis may influence the outcome of infection by reducing virus titres locally; indeed, antiviral activity may account
for the high survival rates observed in a mucosal model of flavivirus infection after intravaginal inoculation of a viral dose that is lethal by all other routes. In this model, large numbers of DC accumulate just beneath the epidermal site of infection, essentially separating infected epithelium from uninfected stroma below (Burke et al., 2004). Interestingly, CCL2 is also strongly expressed at this site (King, Unpublished observations).

4. Entry into the CNS

Virus undoubtedly spreads via the bloodstream at some point to further infect peripheral organs, including the CNS, where neurons are the main target (Xiao et al., 2001; Shrestha et al., 2003; Cheeran et al., 2005; Samuel & Diamond, 2009). However, the factors controlling these phases of virus spread are virtually unknown. The blood of acutely viremic human donors shows substantial increases in IFN-γ and α as well as IFN-stimulated CXCL10 and CCL2. This upregulation of cytokines and chemokines occurs before IgM seroconversion and is therefore argued to be involved in the initial response to acute viremia. On the other hand, this could be the result of chemokine gradients from the WNV-infected brain, since both chemokines are increased in the WNV-infected brain (Klein et al., 2005; Getts et al., 2008). Upregulated IL-4 was also detected in the same time frame, implicating IL-4 in early modulation of immune responses (Tobler et al., 2008).

How virus gains entry into the CNS is still unclear. In some models it is argued that breakdown of the blood-brain barrier (BBB) enables virus entry into the CNS. Toll-like receptors, TLR3, 7 and 8, are responsible for detecting RNA products of viral replication and although TLR3 and 7 are protective against WNV (Daffis et al., 2008; Town et al., 2009; Daffis et al., 2008), TLR3 has also been implicated in aiding entry of WNV into the brain. TLR3 knockout mice have less BBB leakiness and significantly lower viral levels in the brain than wild type mice, with higher viral loads in the periphery, thought to be due to reduced production of TNF, a cytokine strongly implicated in BBB breakdown (T. Wang et al., 2004). Interestingly, macrophages isolated from young humans show a marked reduction in TLR3 levels during WNV infection, while those from elderly donors do not. TLR3 levels are controlled by a signal transducer and activator of transcription 1 (STAT1)-mediated pathway, which is downregulated by WNV E-protein in cells from young, but not elderly donors. Cells from elderly donors produced increased levels of inflammatory cytokines, including TNF (Kong et al., 2008), supporting the notion that TLR3 may play a role in immunopathology in the elderly, ironically via an overly aggressive immune response to WNV. Endothelial tight junction proteins (TJP), such as ZO-1 and claudin-1, are crucial components of BBB integrity and this seal is maintained, inter alia, by astrocytes, non-neuronal support cells of the CNS that are susceptible to WNV infection in vitro (Y. Liu et al., 1989; Cheeran et al., 2005; Verma et al., 2010). WNV-infected astrocytes increase matrix metalloproteinase (MMP) production to degrade TJP (Verma et al., 2010). However, astrocyte infection in vivo has not been reported and furthermore, BBB breakdown is quite variable in flavivirus infection (T.H. Liu et al., 2008; Verma et al., 2010). Alternative ways in which virus could cross the BBB include endothelial transcytosis and/or endothelial infection (German et al., 2006). However, there are few if any reports of endothelial infection itself in vivo by flaviviruses. Moreover, in 167 mice examined at various timepoints after intraperitoneal infection, where significant viremia occurs within 6 h of inoculation, we saw unequivocal endothelial infection only once (King, Unpublished).
Trojan horse transmission into the brain by infected monocytes remains a possibility. Macrophages are susceptible to WNV infection (Cardosa et al., 1986; Shen et al., 1995a; Rios et al., 2006) and could be a crucial cell type contributing to transmission of virus into the brain. However, this has not been shown, and in our hands, while both human and mouse monocytes are readily infectable in vitro, they also very effectively control flavivirus infection, a point further supported in vivo by the lack of infected microglia (or for that matter, infiltrating macrophages) in flavivirus encephalitis (Getts et al., 2007; Getts et al., 2008). A recent study has shown that neutrophils, recruited to the intraperitoneal infection site in large numbers by CXCL-1 and -2 produced by WNV-infected macrophages, exhibited much higher viral loads than macrophages. The removal of these chemokines or depletion of neutrophils prior to WNV infection resulted in delayed death of animals and reduced viral levels, suggesting a possible role for neutrophils as reservoirs for viral replication and dissemination during the early stages of WNV infection (Bai et al., 2010). However, of the leukocytes attracted to the brain after intranasal infection, less than 3% are neutrophils (King, Unpublished).

The intranasal route of infection enables the separation of systemic anti-viral responses from those mediated by the CNS. Thus, insignificant numbers are in and of themselves attracted to the brain during infection, making it unlikely that they are a primary source of virus in neuroinvasion, although they may be a source of spread to other organs. Notwithstanding the susceptibility of most cells to in vitro infection with flaviviruses, it has yet to be convincingly demonstrated that cells in the brain parenchyma other than neurons become infected in vivo. This begs the question of how infected macrophages and neutrophils specifically contribute to neuronal infection. Furthermore, infection via a Trojan horse scenario would presumably occur only if infected leukocytes or monocytes were attracted by chemotactic signals originating in the parenchyma of the brain, whether or not the BBB was intact. This assumes a response to infection, either directly, e.g., via infected neurons producing CCL2 (Getts et al., 2008), or indirectly via other leukocytes already attracted by infection producing chemokines that in turn attract infected neutrophils and monocytes, i.e., once the immune response is well and truly under way. Increases in virus in the brain temporally consistent with this scenario have not to our knowledge been reported.

In vitro cellular adhesion molecules like E-selectin, VCAM-1 and ICAM-1 are upregulated in WNV infection and could support the extravasation of leukocytes into the brain (Shen et al., 1997). Expression of ICAM-1 and VCAM-1 is clearly increased on cerebrovascular endothelium in WNV-infected mice in vivo and this is also associated with infiltration of large numbers of macrophages and microglia into the brain (Figure 1). In primary human brain microvascular endothelial cells, an increase in VCAM-1 and E-selectin is induced when viral replication is at its highest (Verma et al., 2009). Together with TLR3-mediated BBB breakdown, upregulated adhesion molecules could facilitate the infiltration of infected leukocytes into the CNS. However, it is worth noting that WNV-infected IFN-γ knockout mice upregulate cerebrovascular endothelial ICAM-1 and VCAM-1 expression significantly, but have substantially fewer immigrant leukocytes than wild type mice (King, Unpublished). Moreover, although WNV induces BBB permeability in some models, it may not be the primary route of entry into the CNS. Mice and hamsters infected with WNV exhibited signs of BBB leakiness at the same timepoint they succumbed to virus, indicating that infection of the brain began prior to the BBB becoming compromised (Morrey et al., 2006; Morrey et al., 2008) (King, Unpublished). Similarly, in TBEV infection in mice, BBB breakdown occurs 2-3 days after virus is detectable in the brain (Růžek et al., 2011).
There is however, good evidence of centripetal nerve spread from the periphery (Engle & Diamond, 2003; Hunsperger & Roehrig, 2006; Getts et al., 2007). In the footpad model, viral infection occurs in the dermal layer of the epithelium in the footpad, which is enervated by sensory fibres of the dorsal root ganglion (DRG) of the peripheral nervous system (PNS). In vitro, PNS neurons support WNV infection and in mice the DRG is highly susceptible to WNV infection, suggesting that it may be involved in retrograde axonal transport of virus from the PNS to CNS (Hunsperger & Roehrig, 2005, 2006). This is consistent with our own studies using intraperitoneal inoculation of WNV in mice, where WNV is seen in the cervical spinal cord 1-2 days before it is seen in the brain parenchyma, spreading in a caudal to rostral manner. In contrast, intranasal infection results in rostral to caudal spread through the brain, with spread to various anatomical regions via known neural connections (King, Unpublished). If the sciatic nerve of golden hamsters is transected above the infection site, a systemic infection with less severe clinical symptoms of CNS invasion occurs (Samuel et al., 2007), denoting a contribution to spread by intact axons. Treatment of mice with nocodazole, a microtubule inhibitor that prevents retrograde axonal transport, prior to inoculation, delays virus spread to the CNS by 6 days (Hunsperger & Roehrig, 2009). However, taken together, it is likely that more than one pathway is involved in WNV spread to the CNS, with inoculation site, dose, age and genetics all influencing this.

Fig. 1. WNV infection results in the upregulation of ICAM-1 and VCAM-1 on brain vasculature in WNV encephalitis. Green = macrophages and microglia (lectin staining), Red = ICAM-1 (top right), VCAM-1 (bottom right) Blue = DAPI. Left panels = mock-infected, Right panels = d7 WNV-infected
5. CNS infection

_In vitro_, virions attaching to the plasma membrane enter cells via clathrin-mediated endocytosis to form endosomes. A lysosomal, pH-dependent fusion mechanism expels the nucleocapsid into the cytoplasm in close proximity to the ER where the virus is thought to replicate (Chu & Ng, 2004). All cells of the CNS are readily susceptible to WNV infection _in vitro_ within 16-24 h, including neurons, Schwann cells and astrocytes, although microglia are more resistant (Y. Liu et al., 1989; Argall et al., 1991; Shrestha et al., 2003; Cheeran et al., 2005). In contrast, in animal models, detectable infection is seen in the brain between d3 and 6 post infection (p.i.), depending on the model, with virus in all cases evidently replicating exclusively within neurons, a behaviour distinguishing it from the encephalitic DNA viruses (Steele et al., 2000; Xiao et al., 2001; King et al., 2003; Shrestha et al., 2003; Getts et al., 2007; Brehin et al., 2008). Antibody labelling of monkey brain sections for neuron-specific endose, glial fibrillary acidic protein and WNV were argued to indicate WNV infection of both glia and neurons, but this interpretation is not well supported by the examples provided (He et al., 2009). In humans, viral antigen is found in neuronal cytoplasm and processes, usually at the centre of microglial nodules (Sampson et al., 2000; Guarner et al., 2004).

![Fig. 2. Virus titres in the WNV-infected brain. IN = intranasal, IP = intraperitoneal infection](https://www.intechopen.com)
humans, WNV seems to affect the brainstem and anterior horn of the spinal cord (Sejvar et al., 2003; Guarner et al., 2004). Neuroinvasion also occurs in animals that do not succumb to infection (Hunsperger & Roehrig, 2006; Appler et al., 2010). Damage to neurons can result from either excessive virus replication or an over-exuberant immune response, or both, with death ensuing in either eventuality. Increases in CD45+ leukocyte numbers as well as viral antigen are associated with areas of neuronal injury, degeneration by apoptosis and onset of encephalitis, making it difficult to distinguish between viral and immune-mediated injury (Xiao et al., 2001; Shrestha et al., 2003; Brehin et al., 2008). In general, mice die soon after seizures become evident; if seizures can be suppressed, then survival may be extended several days and virus growth in the brain increases by a further 10-fold or more (Getts et al., 2007). This indicates that the neurons are capable of supporting much higher levels of virus replication than is usually evident at death. Microglial nodules, perivascular cuffing, principally comprised of infiltrating macrophages and T cells, and in advanced disease, neuronal loss, are prominent among the neurohistopathological and immunohistochemical findings (Steele et al., 2000; Guarner et al., 2004; Petzold et al., 2010). Significant leukocyte infiltration seems to occur around d5 p.i., irrespective of the model used, associated with full activation of the adaptive immune response.

Cells of the CNS each respond differently towards infiltrating virus. In vitro one of the responses to viral infection of astrocytes and microglia is the production of chemoattractants like CCL5 and CXCL10 (Cheeran et al., 2005), which recruit T cells and possibly monocytes; both astrocytes and microglia can produce CXCL9, which similarly attracts T cells (Muller et al., 2007) (Getts, Unpublished). Infected neurons produce copious amounts of CCL2, which recruit macrophages and microglia from the bone marrow (Getts et al., 2008). IFN-γ plays an important role in the formation of the seizure cascade during the development of the CNS, as IFN-γ knockout mice do not develop seizures during WNV infection. Seizures cannot be recapitulated by IFN-γ-producing T cells infiltrating into the brain in WNV-infected IFN-γ knockout chimeras previously reconstituted with wild type bone marrow. The role of the glutamate receptor, N-methyl-D-aspartate in the development of these seizures has also been shown (Getts et al., 2007). While it is clear that many soluble factors are produced in the brain, it is not so obvious which cells produce them in vivo. Much work will be required to fully characterise the sequence of inductive and inhibitory interactions between local cells, infected cells and immigrant leukocytes.

6. Microglial activation

Microglial activation is clearly associated with virus infection of neurons rather than immune leukocyte infiltration. After intraperitoneal inoculation, WNV can be seen in the brain by d6 p.i., when activated microglia are first observed, one day after leukocyte infiltration is first evident. However, in the intranasal model, microglial activation is seen at d3 p.i. when virus is first observed, while leukocyte infiltration is still seen first at d5 p.i., as in the intraperitoneal model (Getts et al., 2008) (King, Unpublished). Microglia form nodules around infected neurons soon after infection (King et al., 2003; Guarner et al., 2004; Petzold et al., 2010), presumably recruited by the soluble factor outputs from infected neurons, including CCL2. Consistent with this, microglia, at first dendritic, quickly lose these normal projections to assume a more motile amoeboid phenotype.
(Getts et al., 2008). Interestingly, as the number of infected neurons increases, these nodules become less apparent, perhaps because the concentrations of these soluble factors reach a virtual equilibrium within the brain, thus abrogating the concentration gradients likely required for nodule formation (King, Unpublished). Whether the formation of nodules is protective or damaging to neurons is not known, but relatively few infected neurons at the centre of microglial nodules are TUNEL-positive in WNV encephalitis (Getts et al., 2007). There is a significant increase in microglial numbers in the brain during infection, with a decrease in resting microglial numbers. This increase is accounted for by bone marrow-derived monocyte immigration and is not due to in situ proliferation of microglia (Getts et al., 2008). Whether immigrant microglia subsequently return to a resting state in the brain if the host survives and/or whether these cells have a role in the causation of any subsequent neurological sequelae, remains to be elucidated.

Fig. 3. Flow cytometry showing infiltration of macrophages and microglia in the WNV-infected and mock-infected mouse brain. R1 (green profile at right) = CD45$^{\text{lo-int}}$ microglia (mock-infected), R2 (red profile at right) = CD45$^{\text{lo-int}}$ microglia (WNV-infected), R3 (blue profile at right) = CD45$^{\text{hi}}$ macrophages (WNV-infected)

Usually by d6 p.i. the whole microglial population in the brain is activated and this can be detected as an increase in CD45 expression by flow cytometry (Figure 3) and by their amoeboid morphology using lectin immunohistochemistry (Brehin et al., 2008; Getts et al., 2008). Similar to infiltrating macrophages, activated microglia in the WNV-infected brain also express higher levels of Ly6C, compared to mock-infected mice. In Rhesus monkeys infected intracerebrally with three antigenically divergent flaviviruses, activated microglia are identified by their enlarged morphology, short thicker processes and CD68 expression. In this model, microglia are found next to dying neurons and neuronal debris where they perform a phagocytic function (Maximova et al., 2009). They also secrete various proinflammatory mediators and cytokines as part of the response to local and systemic infection. The increased microglial production of leukocyte-recruiting chemokines, CXCL10 and CCL2, is triggered by the activation of the p53-mitogen-activated protein kinase and extracellular signal-regulated kinase intracellular signaling pathways by WNV infection (Cheeran et al., 2005). Neutralisation of CCL2 by antibody on d6 p.i., results in prolonged survival, strongly implicating microglia as contributors to fatal neuropathology (Getts et al., 2008).


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Encephalitis is an inflammation of the brain tissue associated with clinical evidence of brain dysfunction. The disease is of high public health importance worldwide due to its high morbidity and mortality. Flaviviruses, such as tick-borne encephalitis virus, Japanese encephalitis virus, Murray Valley encephalitis virus, or St. Louis encephalitis virus, represent important causative agents of encephalitis in humans in various parts of the world. The book Flavivirus Encephalitis provides the most recent information about selected aspects associated with encephalitic flaviviruses. The book contains chapters that cover a wide spectrum of subjects including flavivirus biology, virus-host interactions, role of vectors in disease epidemiology, neurological dengue, and West Nile encephalitis. Special attention is paid to tick-borne encephalitis and Japanese encephalitis viruses. The book uniquely combines up-to-date reviews with cutting-edge original research data, and provides a condensed source of information for clinicians, virologists, pathologists, immunologists, as well as for students of medicine or life sciences.

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