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Virus-Induced Encephalitis and Innate Immune Responses – A Focus on Emerging or Re-Emerging Viruses

Melanie Denizot[1], Vincent G. Thon-Hon[1],
Shiril Kumar[1], Jim W. Neal[2] and Philippe Gasque[1]
[1]*GRI/IRG, Immunopathology and Infectious Disease Research Grouping (IRG, GRI), EA4517, University, CHR Felix Guyon and CYROI of La Reunion*
[2]*Neuropathology Laboratory, Dept of Histopathology, Cardiff University Medical School., CF14 4XN*
[1]*France*
[2]*UK*

1. Introduction

A wide variety of emerging and re-emerging viruses (e.g. arboviruses, 'arthropod-borne viruses') contributes to neurological diseases. Infections can be associated with new viral variants that are more efficiently transmitted and lead to massive outbreak and increased reports of complicated cases involving the CNS (Tsetsarkin et al., 2007; Vazeille et al., 2007). It is also possible that viruses may have acquired increased neurovirulence by a previously non-neurotropic virus. Viruses that appear to have recently become more neurovirulent include for example the West Nile flavivirus (WNV), Chikungunya alphavirus (CHIKV) and the enterovirus 71 (ENV71) (Griffin, 2010). In addition to these newer challenges, Japanese encephalitis flavivirus (JEV), rabies, polio, measles virus (MV), human immunodeficiency virus (HIV) and human herpes virus (HHV) remain important causes of neurologic diseases. Focusing on CHIKV, this is an alphavirus of the *Togaviridae* family transmitted by mosquitoes of the Aedes (*Ae*) genus. The alphavirus group comprises 29 viruses, six of which of the 'Old World, ie Africa' can cause human joint disorders (arthralgia evolving to arthritis), namely CHIKV, O'nyong-nyong virus (ONNV), Semliki forest virus (SFV), Ross River (RRV), Sindbis virus (SINV), Mayaro virus (MAYV) while the so-called 'New World' such as Eastern equine encephalitis virus (EEEV) and Venezuelan equine encephalitis virus (VEEV) can cause severe brain damage (Das et al., 2010; Jaffar-Bandjee et al., 2009). Interestingly, CHIKV-associated neuropathology was first described in the 1960s but it is the unprecedented incidence rate in the Indian Ocean with efficient clinical facilities that allowed a better description of cases with severe encephalitis, meningoencephalitis, peripheral neuropathies and deaths among newborns (mother-to-child infection), infants and elderly patients (Das et al., 2010; Jaffar-Bandjee et al., 2009). The follow-up of the neonates contaminated by CHIKV clearly indicates poor outcomes and neurodevelopment defects (Jaffar-Bandjee et al., 2011). Neurological manifestations described in adults requiring hospitalization involved cases of encephalopathy frequently associated

with the presence of IgM anti-CHIKV in the CSF, encephalitis, Guillain-Barre, encephalomyeloradiculitis and rare deaths (Economopoulou et al., 2009; Lemant et al., 2008). In recent histopathological studies, CHIKV infection in adults was associated with bilateral frontoparietal white matter lesions with restricted diffusion, which is described as an early sign of viral encephalitis (Ganesan et al., 2008). Focal perivascular lymphocytic infiltrates were also present in area of active demyelination and some degree of microglial activation was also noted in the gray matter which may contribute to bystander neuronal loss (Ganesan et al., 2008). Although data are still scarce, the number of cases with CNS involvement appears to support the neurotropic/neuroinfectious activity of CHIKV. This unique CNS infection illustrated by subventricular white matter lesions and intraparenchymal haemorrhages have been confirmed experimentally. CHIKV diseases can be reproduced in several animal models and the virus was shown to infect mouse/macaque brains and to replicate in cultures of glial and neuronal cells (Gardner et al., 2010; Labadie et al., 2010; Solignat et al., 2009; Wang et al., 2008; Ziegler et al., 2008). The incidence of neuroinfection is dramatically increased following either the injection of high viral titers, the route of injection (intranasal > intraperitoneal), in young animals (less than two week-old) or in mice failing to mount a robust interferon response (i.e. IFNAR knockout animals). Thus, experimental infections where mice were inoculated subcutaneously showed rapid and robust replication (10^6-10^7 PFU/ml) of CHIKV in the brain particularly of newborn mice. Interestingly, infected mice showed signs of illness suggestive of human clinical pathology such as loss of balance, difficulty of walking, dragging of the hind limbs, skin lesions but with rare mortality. CHIKV neuroinfection is particularly severe in IFNAR -/- mice and targets the leptomeninges, the choroid plexus and ependymal cells lining the subventricular zone (SVZ) also known as one of the neural stem cell niche in adult brains. The nature of the receptor(s) mediating cell attachment and infection remains to be characterized but the role of apoptotic blebs carrying the virus from cell to cell has recently been established as in a Trojan-horse paradigm (see below). On the one hand, the local innate immune response is the key to the control of viral infection but could also, on the other, contribute to neuronal loss through the uncontrolled release of cytotoxic inflammatory cytokines, complement proteins or proapoptotic molecules (TNF-α, FasL, granzymes) (Hauwel et al., 2005). We will review herein the pathological mechanisms as well as the innate immune mechanisms engaged during encephalitis and with special emphasis on chikungunya.

2. Encephalitis and clinical manifestations

The clinical hallmark of acute viral encephalitis includes classically fever, headache, and altered level of consciousness. Other associated clinical observations are disorientation, behavioral and speech disturbances and seizures. These clinical signs distinguish a patient with encephalitis from one with viral meningitis, who can have headache, nuchal rigidity, and fever (Whitley and Gnann, 2002). Clinical findings reflect disease progression and the specific areas of CNS involvement, which is determined by the tropism of different viruses for different cell types expressing different viral receptors. Neurons are most likely to be targeted by several viruses such as polioviruses which preferentially infect motor neurons and rabies which selectively infects neurons of the limbic system (Griffin, 2010). Oligodendrocytes, the myelin-forming cells can also be infected (e.g. HHV6, SFV) and leading to direct or indirect demyelination (Fazakerley et al., 2006; Mock et al., 1999). Other

cells within the CNS can also be the site of viral replication and for instance with mumps virus which can infect epithelial cells of the choroid plexus. The involvement of ependymal cells of the SVZ can result in hydranencephaly following infection for instance by adenoviruses or coxsackie viruses.

Viruses vary greatly in their capacity to induce encephalitis. For some viruses (e.g. mumps), neuroinfection is a common but a relatively benign part of the syndrome.

For others (flaviviruses such as JEV or WNV), although the infection is highly asymptomatic, CNS infection when it occurs is the most prominent clinical feature. A third group of viruses are those which commonly cause infection, but only rarely cause encephalitis (herpes simplex virus, HSV or CHIKV). In this group, newborns and elderly patients are at risk because they either have a poor or inappropriate immune response against the infectious challenge (Hoarau et al., 2010).

A paramyxovirus isolated from a Malaysian patient with encephalitis showed *in vitro* characteristics similar to Hendra virus (HeV), a new morbillivirus previously isolated from horses and human in 1995. Subsequent virological studies have shown that the Malaysian pathogen, now named Nipah virus (NiV), is closely related to, but distinct from HeV and that the two belong to a new genus within the family paramyxoviridae capable of causing major outbreaks of encephalitis. Patients present with fever, headache, dizziness, vomiting, and altered mental state.

Finally, there are viruses for which human infection inevitably and exclusively results in CNS disease (e.g. rabies). In addition to acute pathology, other viruses (e.g. measles) can cause syndromes of post-infectious encephalopathy with the capacity of the virus to hide into tissue sanctuaries. The capacity of these viruses to reactivate the viral cycle is poorly understood and may be the results of immune escape mechanisms.

3. Molecular and cellular mechanisms for virus entry into the CNS

The clinical manifestations of many virus infections are dependent on whether or not virus gains access to susceptible cells within the CNS. Therefore, the mechanisms by which viruses penetrate the CNS are of prime importance in understanding the pathogenesis of the disease. To understand the invasion process it is necessary to describe one of the defensive structures that prevent microbial invasion. The CNS is enclosed completely by three different but connected blood-brain interfaces (Abbott et al., 2010).

A blood -brain barrier (BBB) composed of brain micro-vascular endothelial cells (BMEC) with intercellular tight junctions and supported by astrocytes, pericytes and the basement membrane. The second is highly vascularized and fenestrated barrier localized at the choroid plexus between blood and cerebrospinal fluid (CSF), which also allows passage of some blood components and, thirdly, an interface provided by avascular arachnoid epithelium, underlying the dura, and completely enclosing the CNS (Abbott et al., 2010; Weiss et al., 2009).

There are at least four different mechanisms by which viruses can gain access into the CNS. First, viruses may gain access by infecting the BMEC or may be transported across the BMEC (Jarvis and Nelson, 2002). Infection of the BMEC may provide a portal for viral entry into the CNS and disrupting the BBB function. A number of viruses such as cytomegalovirus (CMV) (Jarvis and Nelson, 2002), HIV (Moses et al., 1993) and arboviruses (Dropulic and Masters, 1990) are able to infect the BMEC at least *in vitro*. In acute viral

encephalitis, capillary and endothelial inflammation of cortical vessels is a striking pathological finding, occurring primarily in the grey matter or grey white junction and this observation may facilitate virus entry. For example, HIV may gain access to CNS *in vivo* by this paracellular route as a result of endothelium activation by TNFα and other proinflammatory cytokines (Fiala et al., 1997).

Second, viruses may transmigrate across the BBB within virally infected leukocytes. For HIV, several studies suggest that virus shedding from infected CD4+ T cells, macrophages, and monocytes during migration through the BBB can instigate CNS replication into the parenchyma (Nottet et al., 1996; Persidsky et al., 1997; Schmidtmayerova et al., 1996). CMV can also be transferred to CNS by virus infected mononuclear phagocytes and bi-directional cell to cell transmission between infected monocytes and endothelial cells (Drevets and Leenen, 2000).

Third, viruses can also penetrate the CNS by taking advantage of incomplete closure of the BBB. Despite the intercellular tight junctions between the capillary endothelial cells in most regions of the BBB, certain areas of the CNS such as the choroid plexus, posterior pituitary, and circumventricular organs are not completely protected by the BBB due to a fenestrated endothelial cell layer and sparse basement membrane (Zhang and Tuomanen, 1999). A number of blood-borne viruses including mumps (Herndon et al., 1974), HIV (Bagasra et al., 1996) and CHIKV (Couderc et al., 2008) have been suggested to penetrate across the choroid plexus micro- vessels and infect the epithelium. In the CSF space, viruses can subsequently infect the ependymal cells and the surrounding brain tissue.

Finally, viruses can spread to the CNS through peripheral neuronal routes, like the motor neurons of the spinal cord ,olfactory neurons, retinal neurons, oculomotor neurons and trigeminal nerves , which are directly connected to the CNS, thus providing a convenient route for neurotropic viruses (Mori et al., 2005; Tirabassi et al., 1998). Viruses including HSV (Barnett et al., 1993), rabies virus (Jackson, 2003) and VEEV (Charles et al., 1995) are able to replicate within peripheral nerves and are transported into the CNS from the PNS along axons as the result of axonal transport of neurons. Certain enteroviruses can also spread to the CNS by infecting enteric neurons (Morrison and Fields, 1991). Virus spread within the CNS by retrograde, anterograde or cell to cell diffusion mechanisms.

4. Infection and replication of viruses in brain cells

4.1 Primary receptors used by viruses to infect CNS cells

The presence of cell membrane proteins that act as virus receptors determines whether a cell can be invaded by a virus or not. Dependent on the receptor(s) chosen, some viruses may infect nearly all mammalian cell types or only a small subset of cells from certain species. We herein have chosen to highlight only some of the receptors used by a few emerging or re-emerging viruses to infect specific cell types in the brain and to cause encephalitis. Several comprehensive reviews have discussed the role of different receptors for rabies (Acethylcholine nicotinic receptors, NCAM CD56 as well as the P75 neurotrophin receptor, NTR) (Lafon, 2005) and, hence, this aspect will not be discussed herein.

4.1.1 Nectin-1 and 2 are cellular receptors for HSV

Nectins are immunoglobulin (Ig)-like Cell Adhesion Molecules (CAMs) involved in the formation of various intercellular junctions and the establishment of apical-basal polarity at cell-cell adhesion sites (Takai et al., 2008). The nectin family which comprises 4 members,

nectin-1 or poliovirus receptor related 1 (PRR1 also called HveC, CD111, HIgR), nectin-2 (also termed PRR2, HveB, CD112), nectin-3 and nectin-4. Each of them contains an extracellular region with three Ig-like domains, a single transmembrane region, and a cytoplasmic tail region. Nectin-1, -2 and -3 are expressed ubiquitously in multiple cell types such as epithelia, fibroblasts and neurons, whereas nectin-4 is mainly expressed in the human placenta. Nectin-1 and -2 have been identified as HSV entry mediators (Hve) **(see Table 1)**. Nectin-1 can serve as entry receptors for both HSV-1 and HSV-2 (Geraghty et al., 1998). In contrast, nectin-2 has more limited entry activity. Indeed, human nectin-2 is only a weak entry receptor for HSV-2 and certain strains of HSV-1 carrying out mutations in the glycoprotein D (Lopez et al., 2000). A more recent study also assessed the roles of the two known entry receptors, HVEM and nectin-1, in neuronal infection in the CNS and the development of encephalitis in a mouse model (Kopp et al., 2009). Intracranial injection of HSV was performed directly into the hippocampus of Wild-type (WT), HVEM KO, nectin-1

Name	HSV	Rabies	HIV	Polio	WNV	CHIKV
Virus family	Alpha herpesvirus	Rhabdovirus	Retrovirus	Picorna virus	Flavivirus	Alphavirus
Genome	(+)DNA double stranded linear	(-)RNA single stranded linear	(+)RNA single stranded linear	(+)RNA single stranded linear	(+)RNA single stranded linear	(+)RNA Single stranded linear
Envelope	yes	yes	yes	No	yes	yes
Route of brain entry	Trigeminal Nerve Olfactory nerve	Retrograde axonal	Cell mediated BBB crossing	Retrograde Axonal + BBB crossing	Direct BBB crossing	Blood- CSF crossing
Receptors	Nectin-1, Nectin-2, HSPG	NCAM (CD56) AChR P75 NTR	CD4, CCR5, CXCR4	Nectin-1(PRR1), Nectin-2(PRR2)	DC-SIGN (myeloid cells)	Apoptotic bleb-mediated cell entry
Targets (CNS)	Neurons	Neurons	Myeloid cells microglia	Neurons	Myeloid cells Microglia	Epithelial cells Ependymal cells Neurons Glia
Clinics	Encephalitis Herpetic neuralgia Meningitis Myelitis	Guillain Barre like syndrome Progressive encephalitis paralysis	Dementia Encephalitis Myelitis Neuropathy	Paralysis Respiratory arrest	Encephalitis Meningitis Myopathy	Encephalopathy Encephalitis Guillain Barre
Geographic distribution	Worldwide	Europe Asia Africa Americas	Worldwide	India Africa	Europe Americas Africa	Africa Asia India (Europe) (Reunion)

(See text for abbreviation)

Table 1. Encephalitis due to emerging and re-emerging viruses

KO and double KO mice. The results indicated that nectin-1 deficient mice showed no signs of disease after intracranial inoculation, and no HSV antigens were detectable in the brain parenchyma. However, HSV antigens were detected in non-parenchymal cells lining the ventricules. In the double KO mice, the results showed an absence of disease and no detectable expression of viral antigens even in non-parenchymal cells, indicating that infection of these cells in the nectin-1 KO mice was dependent on the expression of HveM.

4.1.2 CD46 is a cellular receptor for HHV6 and measles

CD46 also designated as membrane cofactor protein (MCP) is a member of a family of glycoproteins acting as regulators of complement activation, but has subsequently been shown to link innate immunity to adaptative immunity (Seya et al., 1986). CD46 mediates the inactivation of its natural complement ligands C3b and C4b and acts as a cofactor for serine protease factor I (Lublin et al., 1988). CD46 thus protect host cells from homologous complement attack which could result in extensive cytolysis and widespread tissue damage. Another function of CD46 is to promote T cell differentiation from a helper Th1 to a regulatory Tr1 phenotype, depending on IL-2 concentrations (Cardone et al., 2010). Human CD46 is alternatively spliced into several isoforms, resulting in a varying number of extracellular domains and two different cytoplasmic tails, Cyt1 and Cyt2 (Seya et al., 1999). CD46 seems to be constitutively recycled from the cell surface via clathrin-coated pits and transported to perinuclear multivesicular bodies (Crimeen-Irwin et al., 2003). The importance of CD46 in the homeostasis of the organism is highlighted by its ubiquitous expression on the surface of all nucleated human cells (Liszewski et al., 1991).

Human CD46 is a cellular receptor for Human Herpesvirus 6 (HHV-6) (Santoro et al., 1999) and MV (Dorig et al., 1993). The authors demonstrated that both acute infection and cell to cell fusion mediated by HHV-6 were specifically inhibited by a monoclonal antibody to CD46; fusion was also blocked by soluble CD46. Interestingly, they showed that nonhuman cells resistant to HHV-6 fusion and entry became susceptible upon expression of recombinant human CD46. Concerning the study of MV infection in the CNS, a murine model of MV-induced pathology was developed from several lines of transgenic mice expressing human CD46 molecule with Cyt1 or Cyt2 (Evlashev et al., 2000). The results of their experiments showed that all transgenic mice expressing CD46 protein in the brain were highly sensitive to intracerebral infection by the MV Edmonston strain, in comparison to nontransgenic controls. In addition, the two isoforms of CD46, Cyt1 and 2, are functionally similar in mediating MV entry into the brain.

4.1.3 Ephrins are cellular receptors for Hendra virus (HeV) and Nipah virus (Niv)

The Eph (erythropoietin-producing hepatocellular) receptors are the largest family of tyrosine kinase receptors (TRKs). They interact with cell surface bound ligands, the ephrins (Eph receptor interacting proteins) that are a highly conserved class of proteins with many homologous members. Based on structural differences, two classes of ephrins can be classified: ephrins-A (A1 to A6) are attached to the plasma membrane via glycophosphatidyl inositol (GPI) moiety and ephrins B (B1 to B3) crossing the plasma membrane and possessing a short cytoplasmic tail. Eph receptors have diverse functions, such as widespread effects on the actin cytoskeleton, cell-substrate adhesion, intercellular junctions, cell shape, and cell movement (Egea and Klein, 2007; Himanen et al., 2007; Pasquale, 2005; Pasquale, 2008).

Two independent studies identified Ephrin B2 (EFNB2) as the receptor for HeV and NiV, which are emergent paramyxovirus. Of the ten potential receptor-encoding plasmids they used to transfect non-permissive HeLa cells, only the human EFNB2 plasmid confers HeV fusion permissiveness. They further demonstrated that soluble EFNB2 blocks both viruses fusion in human EFNB2-transfected HeLa cells. They also showed that both HeV and NiV glycoprotein G and EFNB2 soluble protein could be specifically and reciprocally captured by ELISA. In addition, both viruses glycoprotein G were efficiently coprecipitated by EFNB2/Fc.
Another study identified EFNB2 as an entry receptor for NiV (Negrete et al., 2005). The authors also reported that EFNB2 binds to the NiV glycoprotein G. They observed that soluble Fc-fusion proteins of EFNB2 effectively blocked NiV fusion and entry into permissive cell types. Moreover, transfection of EFNB2 into non-permissive cells renders them permissive for NiV fusion and entry. Interestingly they found that soluble EFNB2 inhibited NiV-envelope-mediated infection of microvascular endothelial cells and primary cortical rat neurons. EFNB3 was later discovered as an additional receptor for NiV using the Chinese hamster ovary cell line (CHO-pgsA745) that does not express ephrins endogenously (Negrete et al., 2006). Interestingly, the authors characterized the important conserved Leu-Trp residues in the G-H loop of EFNB2 and B3 that are critical for their binding with NiV glycoprotein G.

4.1.4 Scavenger receptor class B member 2 (SCARB2) and EV71

The concept of scavenger receptors (SCAR) was first described by their ability to bind modified low-density lipoproteins (Goldstein et al., 1979). SCAR can bind a variety of natural/endogenous, modified host, microbial (bacterial, viral, fungal, and parasitic), environmental, soluble or particulates ligands by endocytosis and phagocytosis (reviewed in (Mukhopadhyay and Gordon, 2004)). SCARB2 (also known as lysosomal integral membrane protein II or CD36b like-2) belongs to the scavenger receptor class B subfamily, which also includes SCARB1 and CD36 (Calvo et al., 1995; Eskelinen et al., 2003). SCARB2 is a type III double-transmembrane protein with N- as well as C-terminal cytoplasmic tails and is located primarily in lysosomes and endosomes. SCARB2 participates in membrane transportation and the reorganization of the endosomal-lysosomal compartment (Kuronita et al., 2002). Deficiency of SCARB2 in mice causes ureteric pelvic junction obstruction, deafness and peripheral neuropathy (Gamp et al., 2003). SCARB2 is widely expressed in lysosomes and late endosomes (reviewed in (Eskelinen et al., 2003).
Since its identification in California in 1969 (Schmidt et al., 1974), enterovirus 71 (EV71) has been recognized as a frequent cause of epidemics of hand-foot-and-mouth disease (HFMD) associated with severe neurological sequelae in some cases (Blomberg et al., 1974). EV71 infections can progress to aseptic meningitis, acute flaccid paralysis and fatal encephalitis (McMinn, 2002). A recent paper demonstrated that SCARB2 is a receptor for EV71 (Yamayoshi et al., 2009). The authors showed that EV71 binds soluble SCARB2 or cells expressing SCARB2, and the binding is inhibited by an antibody to SCARB2. Furthermore, expression of human SCARB2 enables normally unsusceptible cell lines to support EV71 propagation and develop cytopathic effects. Yet, the detail of the interaction between EV71 and SCARB2 at the cellular level, resulting in CNS infection has not been identified.

4.1.5 CD4 as the primary receptor for HIV

Human CD4 exhibits a poly-Ig-like domain structure which is homologous to an increasingly large number of recognition molecules, and consists in four tandem variable-

joining (VJ)-like domains (Maddon et al., 1987). The Ig-like domains of CD4 are anchored to the membrane by a hydrophobic segment, and followed by a short cytoplasmic region. CD4 is expressed on the surface of T lymphocytes, monocytes, macrophages, and brain microglia (resident macrophages) (Wyatt and Sodroski, 1998).

HIV invades the CNS early following viral infection but provokes brain disease only years later. During the periods of progressive immunosuppression, neurological disease occurs in 15 to 20% of infected individuals which develop cognitive and motor impairments referred to as the HIV type 1 (HIV-1)-associated dementia complex also termed as HIV-associated dementia or HIV encephalopathy (Janssen et al., 1991; Price et al., 1988). Neurological disease is often associated with a marked depletion of CD4+ T lymphocytes (Navia et al., 1986). It is now know that HIV encephalitis is a common pathological manifestation characterized by monocyte infiltration into the brain, the formation of macrophage-derived multinucleated giant cells, microglial nodules, and demyelination (Sharer et al., 1985).

Considerable amount of data identified CD4 as the main entry receptor for HIV. Previous studies on the two AIDS retroviruses, human T-lymphotropic virus type III (HTLV-III) and lymphadenopathy-associated virus (LAV) helped to characterize the primary cellular receptor involved in HIV infection (Dalgleish et al., 1984; Klatzmann et al., 1984). Dalgleish and colleagues identified receptor-positive cells by assessing induction of multinucleated syncytia and by testing the susceptibility of various cell types to pseudotypes of vesicular stomatitis virus (VSV) carrying envelope antigens of HTLV strains. Their results showed that both VSV (HTLV-I) and VSV (HTLV-II) pseudotypes plated on a variety of cell types whereas the VSV (HTLV-III) was more specific to the two human T-cell lines (JM and CEM) tested. In addition, only cells expressing the CD4 antigen were sensitive to syncytium induction by HTLV-III and infection by VSV (HTLV-III) pseudotypes. After the screening of 155 monoclonal antibodies to T-cell surface antigens for their ability to inhibit the syncytia formation induced by HTLV-III, they demonstrated that pre-incubation of cells with all anti-CD4 antibodies blocked the cell fusion induced by HTLV-III. In another paper published the same year, Klatzman *et al*. (Klatzmann et al., 1984) investigated the relationship between the CD4+ tropism of LAV and the presence of CD4 on T lymphocytes. Similarly to the previous paper on HTLV-III, they reported that pre-incubation of CD4+ T lymphocytes with three monoclonal antibodies directed against the CD4 glycoprotein specifically blocked cell infection by LAV.

It is well documented that efficient entry of HIV-1 into target cells is dependent upon binding of the viral exterior envelope glycoprotein, gp120, to the CD4-amino-terminal domain (McDougal et al., 1986). After the virus binding, the HIV-1 envelope glycoproteins mediate the fusion of viral and host cell membranes to complete the fusion process. The formation of syncytia results in the membrane fusion directed by HIV-1 envelope glycoproteins expressed on the infected cell surface with uninfected CD4-positive cells. Although CD4 expression on a target cell seems to be sufficient for HIV attachment, the fusion process appeared to be more complex.

4.2 Secondary receptors of virus entry

4.2.1 Chemokine receptors CXCR4 and CCR5 as HIV infection cofactors

Chemokine receptors are part of the serpentine GTP-binding protein (G protein)-coupled receptors superfamily that include receptors for hormones, neurotransmitters, paracrine substance, inflammatory mediators, certain proteinases, taste and odorant molecules. All known human chemokines fit within four classes based on the cysteine motifs near the N-

terminus. The two major classes are the CXC chemokines (CXCR1 to CXCR5) in which the first two cysteines are separated by a single residue, and the CC chemokines (CCR1 to CCR9) in which the first two cysteines are adjacent. CXCR4 (also termed fusin, HUMSTSR, LESTR, HM89, LCR1, NPYR, D2S201E) and CCR5 (also known as CKR5, CC CKR5, ChemR13, CMKBR5) are membrane-bound co-receptors for HIV entry. CXCR4 is expressed on neutrophils, myeloid cells (as well as microglia), and particularly on T lymphocytes (Loetscher et al., 1994). CCR5 mRNA expression was detected in lymphoid organs such as the thymus and spleen, and in peripheral T lymphocytes and macrophages (Raport et al., 1996). The first HIV-1 co-receptor was identified with the use of a recombinant vaccinia virus-based construct in which fusion between the HIV gp120 envelope glycoprotein (Env)-expressing cells and CD4-expressing cells would lead to the activation of a reporter gene *Escherichia coli* LacZ (Feng et al., 1996). The screening of a HeLa cDNA plasmid library and subsequent sequence analysis of the insert revealed that the protein was a member of the G protein-coupled receptor superfamily and was designated "fusin". In addition, loss-of-function experiments showed that anti-fusin antibodies blocked cell fusion and infection of primary human CD4+ T lymphocytes. Interestingly, both experiments stressed that fusin functioned preferentially for T cell line (TCL)-tropic rather than for macrophage (M)-tropic HIV-1 isolates. The discovery of fusin provided an impetus for the identification of the M-tropic HIV isolates coreceptor. Several independent reports demonstrated that CCR5 is the major coreceptor for M-tropic HIV-1 strains (Alkhatib et al., 1996; Choe et al., 1996; Deng et al., 1996; Doranz et al., 1996; Dragic et al., 1996). The evidence was based on both gain-of-function studies using recombinant CCR5, and loss-of-function studies with CCR5 chemokines ligands (MCP-1, MIP-1α, MIP-1β and RANTES) as blocking agents. After the discovery of CCR5, it was demonstrated that fusin is a chemokine receptor that specifically recognize the CXC chemokines ligands SDF-1α and SDF-1β (Bleul et al., 1996; Oberlin et al., 1996); fusin was thus renamed CXCR4.

4.2.2 Phosphatidylserine (PS), apoptotic blebs and virus spreading from cells to cells

PS is a phospholipid located on the inner leaflet of the plasma membrane (Williamson and Schlegel, 1994; Zwaal and Schroit, 1997). Its internal positioning is maintained by translocases that catalyze aminophospholipid transport from the external to the internal leaflet of the plasma membrane. The loss of PS asymmetry can occur during several cellular events including cell injury, cell activation or apoptosis (Balasubramanian and Schroit, 2003).

Two apoptotic pathways can be identified; (i) the extrinsic apoptotic pathway is initiated by members of the Tumour necrosis factor (TNF) family of death ligands that bind to TNFR death receptor family members, Tumour Necrosis Factor Receptor –related apoptosis inducing signal ligand (TRAIL) and Fas ligand (FASL). This results in the formation of the Death Inducing Signal Complex DISC at the cell membrane. DISC subsequently interacts with Fas-associated death domain protein (FADD) in caspase 8, pro caspase 3 and this activates caspase 3, resulting in host cell death (Wilson et al., 2009); (ii) The intrinsic apoptosis pathway is dependent upon the activation of host proteins such as tumour suppressor protein P53 by virus infection. This in turn activates BH-3 domain only members of the B cell lymphoma 2 (Bcl-2) family, e.g the pro-apoptotic proteins Bax and Bak. The activation of these two proteins produces pores in the outer membrane of mitochondria with the release of cytochrome C activating caspase 9 and cell death (Danial and Korsmeyer, 2004; Kroemer et al., 2007).

Apoptosis following viral infection is a robust line defence mechanism, since the cell auto destruction appears one of the best ways to limit virus production and spreading (Griffin and Hardwick, 1997). Unequivocally, the expected purpose of this cell suicide in response to infection is to short-circuit the viral expansion and to promote the clearance of dead infected cells by professional phagocytes (Fujimoto et al., 2000; Hashimoto et al., 2007). However, most viruses deal with this defensive reaction and have evolved strategies to evade or delay apoptosis (Teodoro and Branton, 1997).

Under normal cellular conditions, exposure PS serves as a recognition signal for internalization of apoptotic cells or debris. PS-mediated apoptotic clearance is a highly conserved mechanism, occurring in both professional and nonprofessional phagocytes (Henson et al., 2001). Importantly, this process does not elicit an inflammatory response (Savill et al., 2002). "Apoptotic mimicry" or the exposure of PS on the surface of a pathogen provides a signal for virus uptake and may represent a mechanism for viruses to stunt the host inflammatory response and evade immune recognition. Some viruses like CMV or HSV-1 and HSV-2, which acquire their envelopes from intracellular organelles, have externalized PS (Pryzdial and Wright, 1994; Sutherland et al., 1997). A previous study investigated the early apoptotic events in real time in intact live ND7 neuron-like cells following HSV-1 infection (Gautier et al., 2003). The authors demonstrated that infection of differentiated ND7 cells by HSV-1 triggers detectable alterations including PS exposure indicative of physiological changes associated with early stages of apoptosis.

Furthermore, control of the apoptotic process by the viruses is key, either to establish a permanent infection when they are able to block apoptosis, or to facilitate their dissemination and prevent inflammatory and immune response when they are able to control and activate the late phase of apoptosis (Chen et al., 2006). Dissemination of viral particles through the production of apoptotic blebs from host cells could confer protection from the immune system (Chen et al., 2006; Everett and McFadden, 1999). Conversely, it has been proposed that phagocytosis of these pathogen (Sindbis for example) -enriched apoptotic blebs by antigen presenting cells (e.g. dendritic cells) could contribute to a robust and uncontrolled adaptive immune response leading to autoimmunity against self-antigens contained within the blebs (Rosen et al., 1995). In the case of CHIKV, it has recently been evidenced that completion of the apoptotic process is an important element for efficient virus propagation (Krejbich-Trotot et al., 2011). Indeed, CHIKV was revealed to exploit, may be in parallel to classical ways of entry and cell exit, an ingenious way of camouflage in apoptotic blebs to enhance viral spreading to neighbouring cells while being shielded from the immune system.

4.2.3 The C-type lectin receptors and WNV cell entry

The superfamily of proteins containing lectin-like domains is a large group of extracellular metazoan proteins with diverse functions (Zelensky and Gready, 2005). The main function of the calcium-dependent 'C'-type lectins is to interact with pathogen-associated molecular patterns (PAMPs) which are well conserved and expressed by various microorganisms and to internalize these pathogens for processing and antigen presentation (Drickamer, 1995). For instance, C-type lectins contain Carbohydrate Recognition Domains (CRDs) capable of binding to conserved oligosaccharides that are commonly found on the surface glycoproteins of viruses (Cambi et al., 2005). C-type lectins are secreted as soluble proteins or produced as transmembrane proteins. The Mannan Binding Lectin (MBL), present in the plasma, is a member of the collectin family and is an example of soluble protein. MBL is

expressed by monocytes/microglia and possesses a globular carboxy terminal sequence that binds to virus proteins containing mannose molecules. The transmembrane lectins include the Mannose Membrane Receptor (MMR also known as CD206) and the Dentritic Cell-Specific ICAM-3 Grabbing Non-integrin (DC-SIGN also known as CD209) receptor that recognizes "self " intercellular adhesion molecule 2 (ICAM2) and ICAM3 (van Kooyk and Geijtenbeek, 2003). MMR contains eight CRD (Weis et al., 1998). DC-SIGN is a type II transmembrane protein which possesses a single globular-structured CRD. DC-SIGN's CRD is separated from the transmembrane region by a neck domain involved in oligomerization and which regulates carbohydrate specificity. Finally, a cytoplasmic tail is present, which includes internalization motifs and an incomplete immunoreceptor tyrosine-based activation motif (ITAM). Microglia, perivascular macrophages and dendritic cells express MMR and DC-SIGN (Burudi et al., 1999; Linehan et al., 1999; Mukhtar et al., 2002; Sallusto et al., 1995; Schwartz et al., 2002). The expression of DC-SIGN on brain microvascular endothelial cells could be advantageous for viral entry into the CNS (Mukhtar et al., 2002).
Two major lineages of WNV, L1 and L2, have been identified after the phylogenetic analyses of glycoprotein E (Lanciotti et al., 1999). L1 strains have a large distribution and have been found in Africa, Europe, the Middle-East, North and Central America whereas the L2 strain is mainly localized in Africa and Madagascar. WNV human infection is usually asymptomatic, however life-threatening neurological disease, including encephalitis or meningitis, generally occurs in older or immunocompromised individuals (Campbell et al., 2002; Granwehr et al., 2004). A recent study investigated the relative contribution of DC-SIGN in infection by glycosylated L1 and non-glycosylated L1 and L2 strains (Martina et al., 2008). The authors showed that in contrast to a non-glycosylated L1 strain, the glycosylated L1 strains use DC-SIGN as an attachment receptor on dendritic cells, leading to enhanced infection.

4.2.4 Heparan sulfate proteoglycans (HSPGs) and HSV

Heparan sulfate proteoglycans (HSPGs) are secreted and membrane associated proteins covalently attached to unbranched glycosaminoglycan heparan sulfate (HS) molecules which are composed of linear polysaccharide chains (Esko and Selleck, 2002). HS molecules are synthesized on a variety of cell surface proteins but are found consistently on members of two major families of membrane-bound proteoglycans: the transmembrane core proteins syndecans and the GPI-linked glypicans (Bernfield et al., 1999). HS can influence cell-environment interactions by binding to a heterogeneous group of growth factors, matrix ligands, and cell surface molecules. The possibility that HS could serve as an entry receptor for HSV type 1 and 2 was assessed on HEp-2 cells (WuDunn and Spear, 1989). They found that heparin blocked both virus adsorption. Different adsorption inhibitory agents including, heparin and poly-L-lysine (both bind to anions on the surface of virions and cells) and platelet factor 4 (which has a high affinity for heparin and heparan sulfate) was tested. After the incubation of these agents with HEp-2 cells either immediately before or during exposure with HSV-1 or HSV-2, an inhibition of virions adsorption by heparin was observed. Same results for poly-L-lysine and platelet factor 4 were obtained. A further study investigated the role of cell surface heparan sulfate in HSV infection using heparan sulfate-deficient mutants CHO cells (Shieh et al., 1992). They demonstrated that CHO mutants with defect in heparan sulfate biosynthesis are resistant to HSV infection and have reduced numbers of receptor for HSV.

5. Innate immune responses against viral infection in the CNS

The active and highly regulated control of immune responses in the brain is referred to as "immune privilege". The BBB, which prevents viruses, constituents of the adaptive immune system and antigen presenting cells, gaining accesses to the brain (for a review, see (Savarin and Bergmann, 2008)), is considered to be responsive for this privileged environment of the CNS. The CNS, therefore relies upon glia perivascular and meningeal cells to provide the innate immune response against virus attack (Hauwel et al., 2005). Microglia, astrocytes, ependymal cells, oligodendrocytes and neurons express Pattern Recognition Receptors (PRR)s (Suh et al., 2009) including the highly conserved Toll like receptors (TLR)s and the Retinoic inducible gene like RIG-1 receptors (RLRs) (Fujita et al., 2007) that detect the presence of "non self "as represented by viral nucleic acids.

5.1 TLRs

The TLRs are PRRs that have unique and essential function in animal immunity. TLRs comprise a family of type I transmembrane receptors, which are characterized by an extracellular leucine-rich repeat (LRR) domain and an intracellular Toll-interleukin-1 receptor (TIR) domain. LRR domains are found in a diverse set of proteins and mediate the recognition of components of foreign pathogens referred to as pathogen-associated molecular patterns (PAMPs) (for a review, see (Alexopoulou et al., 2001)). The cytoplasmic TIR domain of Toll proteins is a conserved protein-protein interaction module that is required for downstream signal transduction. So far, 10 and 12 functional TLRs have been identified in humans and mice, respectively, with TLR1-9 being conserved in both species (Takahashi et al., 2006). Microglia are the resident macrophages in the CNS and also express a wide range of TLRs (TLR1-9). Astrocytes express TLR1, 2, 3, 4, 5 and 9 whereas neurons mainly express TLR3 (Carty and Bowie, 2010). TLRs are located on the cell surface and are also distributed in the endosome so they are strategically placed to detect cytoplasmic viral RNA. TLR9 is activated by DNA rich in CpG motifs, whereas TLR7 and TLR8 recognize RNA viruses and ssRNA. TLR3 is activated by dsRNA formed during replication of viruses. TLRs signal through the adaptor molecules, myeloid differentiation primary response gene 88 (MyD88) and Trif, to initiate intracellular signaling by transcription factors such as and the IFN regulatory factors (IRFs) (Alexopoulou et al., 2001). These IRFs are translocated to the host cell nucleus where they regulate inflammatory cytokine synthesis and stimulate type I interferon synthesis (IFNα-β expression) to produce a protective response (anti-viral state) in adjacent uninfected cells (Paul et al., 2007). A further anti-viral property of the IRF is through its binding to the pro-apoptotic protein Bax and translocation to the mitochondria with activation of the mitochondrial apoptotic pathway, terminating virus replication (Chattopadhyay et al., 2010). Viruses can activate more than one TLR and it is known for example that TLR9 as well as TLR2 in dendritic cells and neuronal cells can respond to HSV to drive a protective IFN-α antiviral response (Bereczky-Veress et al., 2010; Sato et al., 2006). RNA viruses such as HIV, Rabies and WNV are more likely to be recognized by TLR3 and/or TLR7 or 8 expressed by microglia and neuronal cells (Prehaud et al., 2005; Szretter et al., 2010; Wang et al., 2004). The absence of TLR3 enhances WNV mortality in mice and increases viral burden in the brain (Daffis et al., 2008). Compared to wild-type controls, TLR3 -/- mice showed relatively little changes in peripheral viral loads. Interestingly, deficiency of TLR3 was associated with enhanced viral replication in primary cortical neuron cultures and greater WNV infection in neurons after intracranial inoculation while

no significant differences where noted in viral growth kinetics or IFN-alpha/beta induction between wild-type and TLR3 KO fibroblasts, macrophages, and dendritic cells.

5.2 The RIG-I-like receptors (RLRs)

After the discovery of TLRs, several classes of PRRs, including the RLRs were identified. The RLR family consists of the three RNA helicases members: retinoic inducible gene-I (RIG-I), the melanoma differentiation-associated factor 5 (MDA5 also known as helicard or IFIH1) and the laboratory of genetics and physiology 2 (LGP2) that detect RNA viruses (Yoneyama and Fujita, 2009). RIG-I and MDA5 contain a C-terminal DExD/H box RNA helicase domain that is a characteristic amino acid signature motif of many RNA binding proteins, as well as two N-terminal caspase activation and recruitment domain (CARDs). LGP2 lacks CARD domains and has been proposed to function as a regulator of RIG-I/MDA5 signaling (Nakhaei et al., 2009). RIG-1 and MDA-5 are expressed by microglia and astrocytes, and located mainly in the cytosol and detect both short and long ds and ssRNA respectively (Furr et al., 2008; Hoarau et al., 2011). This interaction activates a series of intracellular signaling pathways using the adaptor molecules such as Interferon promoter stimulator (IPS-1) resulting in the transcription of IFNαβ interleukins and a range of anti-viral proteins. IPS-1 is key in the control of cell infection by several alphaviruses and flaviviruses including CHIKV and WNV, respectively. IPS-1-/- mice was recently shown to exhibit increased susceptibility to WNV infection marked by enhanced viral replication and dissemination with early viral entry into the CNS (Suthar et al., 2010). Moreover, infection of dendritic cells macrophages and primary cortical neurons showed that the IPS-1-dependent RLR signaling was essential for triggering IFN response (Suthar et al., 2010). Unexpectedly, infected KO mice also displayed uncontrolled inflammation that included elevated systemic type I IFN, proinflammatory cytokine and chemokine responses, increased numbers of inflammatory cells, enhanced humoral responses marked by complete loss of virus neutralization activity, and increased numbers of virus-specific CD8+ T cells and non-specific immune cell proliferation in the periphery and in the CNS. This uncontrolled inflammatory response was associated with a lack of regulatory T cell expansion that normally occurs during acute WNV infection. Thus, the enhanced inflammatory response in the absence of IPS-1 was coupled with a failure to protect against WNV infection. This is an important finding which stresses that IPS-1-dependent RLR signaling is equally important in the innate/adaptive immune responses but also in the balance of the immune response to WNV infection. With regards to CHIKV, it has recently been shown that IPS-1 is important at least in the periphery to drive a robust anti-viral response (Schilte et al., 2010).

5.3 CNS Innate immune system; Interferon type 1 and 2 responses stimulate an anti-viral response

Mice deficient for the type I IFN receptor (IFNAR) has proved the fundamental importance of the type I IFN in the control of virus replication (Couderc et al., 2008; Muller et al., 1994). Indeed, CNS virus infections are more lethal in mice deficient in IFNAR than the wild type equivalent, emphasizing the importance of IFNα/β/IFNAR pathway for anti-viral defense (Griffin, 2003; Paul et al., 2007). The type 1 interferon response is made by most CNS cells and results in a non-apoptotic anti-viral response by the host cell reducing infection by a replicating RNA virus (Katze et al., 2002). The IFN anti-viral response involves IFN binding to IFNAR on the host cell leading to the activation of Janus kinases (JAK) with phosphorylation of the activators of transcription factors (STAT1 and STAT2). These two

proteins enter the nucleus to drive the expression of interferon stimulated genes (ISGs) (Goodbourn et al., 2000) . Host CNS cells in response to IFN stimulation produces a range of anti-viral ISGs, including oligoadenylate synthetase (OAS) and IFN-inducible ds RNA – dependent protein kinase (PKR) that both modulate virus replication; RNAse L and Mx that inhibit viral transcription together with the RNA deaminases (ADAR-1 and APOBEC3G) producing mutations in viral genomes (Goodbourn et al., 2000) (George et al., 2009) (Toth et al., 2009). (IRFs) IRF-7, IRF-9, and ISG54 are all increased following CNS virus infection and one IRF, ISG15, has been found to be significantly increased in astrocytes following their infection with RNA virus (Paul et al., 2007). Type 2 interferon response is due to the interferon γ again a glycoprotein expressed by activated T cells when TCR binds to their cognate antigen (Goodbourn et al., 2000). Many of the emerging viruses disable the host anti-viral response by targeting the pathways responsible for regulating IFN and anti-viral proteins.

5.4 Phagocytosis and removal of infected cells

The peculiarity of the CNS is that it is composed by a majority of cells that are non-renewable. Hence, it is fundamental to rapidly clear the infected cells and limiting bystander effects and to reduce massive neuronal loss. Apoptotic cells must be rapidly cleared from the CNS because they contain neurotoxic proteins and viruses capable of increasing host tissue infection (Griffiths et al., 2009). Apoptotic cells express a range of non-self-molecules termed Apoptotic cell- associated molecular patterns (ACAMPs) on their surface and these molecules include sugars, nucleic acids, ribonucleoproteins and oxidized low density proteins. The best characterized ACAMP is the phosphatidylserine molecule (PS) (Fadok et al., 1998) (Savill et al., 2002). Glia and macrophages express a range of receptors including the phosphatidylserine receptor (PSR), CD14 and the Scavenger receptors (SR) divided into SRA (SRA-1, SRA-II) and SR B including CD36 all expressed by microglia (Areschoug and Gordon, 2009; Husemann et al., 2002; Savill et al., 2002) which are all involved in the selective recognition and clearance of apoptotic cells. It should be stressed that these receptors may also contribute in turn to the infection of phagocytic cells.

5.5 Autophagy and control of viral infection

Autophagy is a fundamental homeostatic process that leads to the degradation and recycling of long-lived cytoplasmic proteins and organelles (Klionsky, 2007) (Yoshimori, 2004). The hallmark of autophagy is the formation of double or multiple membrane-bound vesicles called autophagosomes, which sequester a portion of the cytoplasm and fuse, after maturation, with lysosomes to digest their contents. In the same way, autophagy can also act directly, as an innate immune actor, to engulf and degrade pathogens. There is now some evidence for an antiviral role of autophagy related to viruses that specifically target neurons. The prototype virus studied was SINV, which is a positive-stranded RNA virus in the alphavirus genus. In mice, SINV produces fatal encephalitis that can be prevented by the cellular Bcl-2, an inhibitor of apoptotis (Levine et al., 1993). In a search to understand the mechanism by which Bcl-2 regulates Sindbis virus pathogenesis, a yeast two-hybrid screening was performed of a mouse brain library using Bcl-2 as bait, leading to the identification of a novel Bcl-2-interacting coiled-coil protein, Beclin 1. Beclin 1 is the mammalian homologue of yeast Atg6 and the first identified mammalian autophagy protein. Enforced neuronal expression of Beclin 1 was found to protect mice against fatal SINV encephalitis. In addition, Beclin reduces CNS SINV replication and viral-induced

neuronal apoptosis (Liang et al., 1998). The ability of enforced neuronal expression of Beclin 1 to protect against lethal SINV encephalitis suggests a protective role for autophagy in host defence against an emerging neurotropic infection.

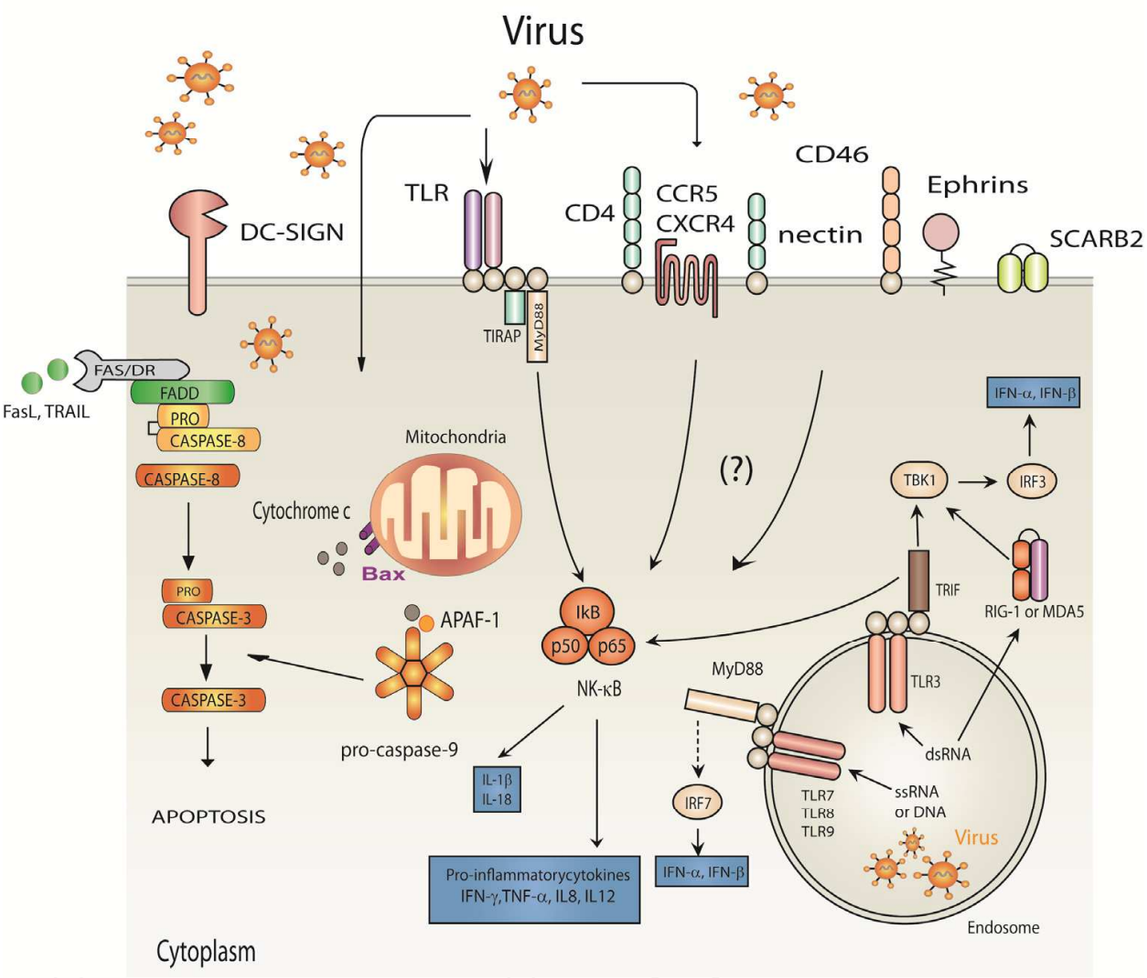

Fig. 1. **Interactions between viruses and host cell receptors**: Several receptors are known to interact with viruses and controling subsequent encephalitis. Some are receptors (e.g. CD4, CD46) involved in cell entry and signaling although the pathways which are engaged remain poorly characterized. Others are innate immune receptors such as RIG-I MDA5 and TLR which are expressed by neurons and glial cells (microglia and astrocyte) to initiate well-described signaling pathways that converge at the activation of the transcription factors (IRF3/7 and/or nuclear factor-kB (NFkB)). These key events lead to the expression of type-I interferons (IFN-α/β). The innate immune signaling pathways are intimately linked to apoptosis. The intrinsic apoptosis pathway is initiated by the release of cytochrome C from the mitochondria which promotes the formation of the apoptosome, including APAF-1 (apoptotic protease activating factor) and caspase 9 which in turn activates the effector caspase 3. The extrinsic pathway mobilized notably by TNF-α, TRAIL or FASL involves death-receptor signaling pathways linked to FADD and caspase 8. Some viruses can escape apoptosis by inducing the expression of anti-apoptotic proteins such as Bcl2.

6. Conclusion

Despite the vast genetic diversity among viruses, these pathogens face similar obstacles on the way into the CNS with the dual role of a physical and molecular barriers of the innate immune system to restrict and protect from infection. However, upon entry whether they are hidden in leukocytes or in apoptotic blebs, they will be free to interact with neurons in a rather 'immunopriviliged' environnement allowing viral persistence. However, this paradigm has been reconsidered with the observation that resident cells possess several of the key innate immune receptors involved in the recognition of the intruders and to engage a salutary antiviral response (IFN). It is now clear that other molecular interactions between the viruses and these host cells expressing primary and secondary signaling receptors will determine the outcome of the infection. Some receptors may control apoptosis or cell differentiation which in turn may have an impact on the capacity to resist viral infection and spreading. Our understanding of the molecular mechanisms of CNS diseases is still in its infancy. Increasingly, identification of virulence factors and host receptors will provide solutions for this complex puzzle. Understanding these interactions will increase our ability to control neuroinvasion and encephalitis. Moreover, it will also teach how to use these entry routes for therapeutic benefit, for example, for gene delivery of therapy of cancer and neurodegeneration.

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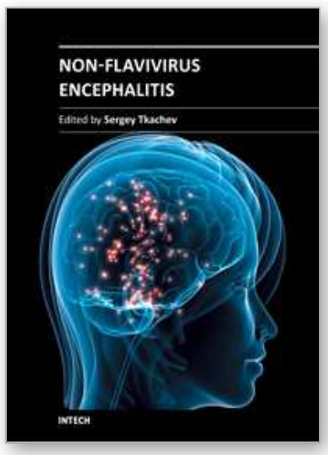

Non-Flavivirus Encephalitis
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This book covers the different aspects of non-flavivirus encephalitises of different ethiology. The first section of the book considers general problems of epidemiology such as study of zoonotic and animal vectors of encephalitis causative agents and methods and approaches for encephalitis zoonoses investigations. The members of different virus species are known to be the causative agents of encephalitis, so the second section of the book is devoted to these viral pathogens, their epidemiology, pathology, diagnostics and molecular mechanisms of encephalitis development by such viruses as HIV/SIV, herpes simplex virus type 1 and equine herpesvirus 9, measles virus, coronaviruses, alphaviruses and rabies virus. The next section of the book concerns the study of protozoan pathogens such as toxoplasma and amoebae. The last section of the book is devoted to multicellular pathogen as human Filaria Loa Loa - a filarial worm restricted to the West Africa.

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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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