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Coronaviruses as Encephalitis - Inducing Infectious Agents

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1. Introduction

Encephalitis usually refers to brain inflammation of various possible causes, including viral infections. Overall, viruses represent the most common cause of encephalitis in humans. The U.S. Center for Disease Control and Prevention (CDC) estimates an annual incidence of usually between 150 and 3000 new cases per year of Arboviral encephalitis in the United States (http://www.cdc.gov/). Although several thousand cases of encephalitis of various viral origins are reported each year, the CDC suspects that many more cases may go unreported. Indeed, encephalitis can follow or accompany common viral illnesses, such as infectious respiratory diseases, and sometimes signs and symptoms of the latter may mask concurrent encephalitis. Most commonly, clinically relevant viral encephalitis affects children, young adults, or elderly patients. The involvement of other determinants, such as the nature of the specific viral agent, the host immune status, and various genetic and environmental factors, is also of importance.

The pathophysiology of viral encephalitis varies according to the virus family involved. Encephalitis occurs in two forms: primary encephalitis involving direct viral infection of the central nervous system (CNS; brain and spinal cord) and secondary encephalitis involving a viral infection which first occurs elsewhere in the body and then travels to the brain. Viruses may enter the CNS through two distinct routes: hematogenous dissemination or neuronal retrograde dissemination. The hematogenous spread, which is the most common path, involves the presence of a given virus in the blood (viremia), where it can either remain free for a period of time or infect leukocytes that will become some sort of viral reservoir. This latter situation, called the Trojan horse, is the route taken by human immunodeficiency virus (HIV) to disseminate to the CNS in humans. Arboviruses also use the hematogenous route to gain access to the CNS, where they can induce a zoonotic encephalitis, with the virus surviving in infection cycles involving bites by arthropods and various vertebrates, especially birds and rodents. After an insect bite, the virus can be transmitted in the blood of a susceptible animal after local replication in the skin.

Another form of viral spread towards the CNS is through retrograde neuronal dissemination, where a given virus infects neurons in the periphery and uses the transport machinery within those cells in order to gain access to the CNS.

Neuroinvasive viruses can damage the CNS as a result of misdirected host immune responses (virus-induced neuroimmunopathology) and/or viral replication, which will

directly induce damage to CNS cells (virus-induced neuropathology). In acute encephalitis, viral replication occurs in the brain tissue itself, possibly causing destructive lesions of the gray matter, as was described after herpes simplex virus (HSV), rabies, or some arbovirus infections. Rabies virus usually spreads to the CNS through retrograde peripheral nerve dissemination and one of the possible routes of HSV spread to the CNS is through the olfactory tracts.

Encephalitis caused by viruses generally can be classified into four different groups. (1) *Arboviruses* which appear to be the primary cause of acute encephalitis (Eastern Equine Encephalitis, Japanese Encephalitis, La Crosse Encephalitis, St. Louis Encephalitis, Western Equine Encephalitis, West Nile Virus Encephalitis). These viruses are transmitted to humans by the bite of infected mosquitoes and/or ticks. (2) *Enteroviruses*, such as coxsackievirus or polioviruses. These viruses spread through the fecal-oral route. Infection can result in a wide variety of symptoms ranging from mild respiratory illness (common cold), to, foot-and-mouth disease, acute hemorrhagic conjunctivitis, aseptic meningitis, myocarditis, severe neonatal sepsis-like disease, and acute flaccid paralysis. (3) *Herpes viruses* constitute another major cause of encephalitis in North America. Members of this virus family include HSV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV). They are highly contagious as they can be spread when an infected person is producing the virus. (4) Other viruses, following childhood viral diseases such as measles, mumps, and rubella can in rare cases develop secondary encephalitis. More recently, respiratory viruses were closely associated with encephalitis as reported for influenza virus (for reviews, see Maurizi, 2010 and Wang et al., 2010) or occasionally for coronaviruses (Yeh et al., 2004).

2. Coronavirus

Coronaviruses are ubiquitous respiratory and enteric pathogens. They also represent one family of viruses that bear neurotropic and neuroinvasive properties in various hosts including humans, pigs, and rodents. Coronaviruses form a group of enveloped, positive-sense, single-stranded polyadenylated RNA viruses that have the largest genome (~30 kb) among RNA viruses. They replicate in the cytoplasm of infected cells using a viral RNA-dependent RNA polymerase that is translated from the genomic RNA very early after viral entry in the host cell. Coronaviruses first target respiratory and mucosal surfaces and then, depending of host and virus strain, may spread to other tissues (brain, eyes, liver, kidneys and spleen) and cause a range of pathologies such as pneumonia, encephalitis, neurodegenerative demyelination, hepatitis, enteritis, and nephritis among others (Resta et al., 1985; Riski & Hovi, 1980).

Human coronaviruses (HCoV) are represented by five different strains; HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1 and the causative agent of the severe acute respiratory syndrome (SARS), named SARS-CoV. Among these five strains, at least HCoV-229E and HCoV-OC43, as well as SARS-CoV possess neuroinvasive properties as viral RNA can be detected in human brains (Arbour et al., 2000; Gu et al., 2005; Xu et al., 2005).

However, these human coronaviruses are not well characterized as to their capacity to invade and infect the CNS. On the other hand, the murine counterpart of HCoV-OC43, which is designated Mouse Hepatitis Virus (MHV), represents one of the best-characterized models of this family. MHV infects mice and rats and some strains are neurotropic and

neuroinvasive, causing a large spectrum of diseases from hepatitis to encephalitis and chronic demyelination (Stohlman & Hinton, 2001; for reviews, see also Bender & Weiss, 2010 and Lane & Hosking, 2010).

2.1 Murine Hepatitis Virus: An agent of encephalitis

MHV exhibits various organ tropisms as well as pathogenic potentials. The most common strains used for pathogenesis studies are the neurotropic MHV-JHM (previously called MHV-4), the hepatotropic/neurotropic MHV-A59 and the hepatotropic MHV-3. Experimental infections of rodents with these strains provide animal models for human diseases such as hepatitis, encephalitis, and demyelinating diseases such as multiple sclerosis. Infection of mice by the intranasal or intracerebral route with MHV-JHM or MHV-A59 serves as a model for studying encephalitis and determinants of neurovirulence.
MHV is part of the family *Coronaviridae* and the genus betacoronavirus. Its genome is 32-kilobases long and comprises different open reading frames (ORFs), which encode four structural proteins: spike (S), envelope (E), membrane (M), nucleocapsid (N), with some strains also expressing a gene encoding two other structural proteins: hemagglutinin-esterase (HE) and internal protein (I). The genome also encodes three nonstructural proteins, which functions remain poorly understood. The assembly of coronavirus virions needs a concerted action of three structural proteins: the membrane protein (M), the small envelope protein (E), and the nucleocapsid protein (N) (de Haan & Rottier, 2005; Masters 2006). Among these three proteins, no role in pathogenesis has been reported for M and E.

2.2 Viral molecular determinants of encephalitis

While the molecular determinants of pathogenesis remain poorly understood, there is evidence that both host and viral factors play a role in coronavirus-induced disease. Experiments completed during the last decade have used infectious cDNA clones to produce viruses of high and low virulence to investigate, by the mean of reciprocal chimeric viruses, the molecular determinants of neurovirulence. Viral genes responsible for high MHV neuropathogenesis contribute to viral spread, replication and activation of innate/adaptive immunity.

2.2.1 Spike glycoprotein: S

The S protein mediates attachment of the virus to its receptor on the target cell and viral fusion with the cell membrane, as well as viral entry and cell to cell spread (Collins et al., 1982; Williams et al., 1991). Based on previous studies, which used numerous variant viruses selected for resistance to neutralizing monoclonal antibodies, an association was made between various mutations or deletions in the S gene and neuroattenuation of the different strains of MHV (Gallagher et al., 1990; Wege et al., 1988). More recently, the use of recombinant MHV viruses with a modified spike (S) glycoprotein has definitively identified the S protein as a major determinant of neurovirulence. The recombinant A59 (rA59) virus which contains the S gene of JHM (S_{JHM}) confers a highly neurovirulent phenotype. The viral infectious dose inoculated into mouse brain to induce a 50% lethal dose (LD_{50}) is decreased by more than 1000-fold, demonstrating the role of S in neurovirulence (Phillips et al., 1999). Neuronal infection has long been proposed to be a major determinant of MHV neurovirulence (Dubois-Dalcq et al., 1982), and the recent use of recombinant viruses demonstrated that even if neurovirulence is increased, cellular tropism remained the same,

as rA59 and rA59/S_{JHM} recombinant viruses target equally neurons and astrocytes (Phillips et al., 2002). The degree of neurovirulence is associated with the degree of spread through the brain. The faster the spread, the higher will be the neurovirulence. This increased viral spread and dissemination also induces a greater immune response to infection. The magnitude of lymphocytic infiltration in mouse brain following infection by rA59 with S_{JHM} and rA59 with S_{A59} is different, as S_{JHM} induced a more efficient CNS invasion of lymphocytes than S_{A59} and a significant increase in the percentage of $CD8^+$ T cells (Phillips et al., 2002). Increased immune-mediated pathology was associated with rapid viral spread (Miura et al., 2008; Wodarz & Krakauer, 2000). The recombinant virus rA59, harboring the JHM S protein (S_{JHM}) is not as virulent as wild-type recombinant rJHM, indicating that neurovirulence also depends on other background genes. The high neurovirulence of JHM is also associated with an increased innate immune response characterized by high numbers of infiltrating neutrophils and macrophages, demonstrated by comparing rJHM bearing S_{A59} to rJHM bearing S_{JHM} during the acute phase of encephalitis (Iacono et al., 2006). Nevertheless, the viral strain background also plays a strong role, as viruses containing the rA59 genes demonstrated markedly increased levels of CD8+ and CD4+ T-cell infiltration compared to the rJHM background-containing viruses (Iacono et al., 2006). Virus-specific $CD8^+$ T cells are critical for protection against neurotropic coronaviruses. On the other hand, the combination of a rapid and extensive spread through the CNS with the lack of induction of a significant T-cell response results in the high lethality of JHM-infected mice (MacNamara et al., 2005; 2008).

2.2.2 Nucleocapsid protein: N

Structural proteins are transmembrane proteins located in the viral envelope, except for the N protein, which is associated with the viral RNA genome (Baric et al., 1988; Sturman et al., 1980). Replacement of the N gene of rA59 with that of JHM (N_{JHM}) confers to the rA59 background a highly neurovirulent phenotype. The viral infectious dose inoculated into mouse brain to induce a 50% lethal dose (LD_{50}) is decreased between 100- and 1000-fold. Inversely, the rJHM with N_{A59} is attenuated, but this is more evident on the attenuated phenotype (rA59/S_{JHM}), indicating that replacing the MHV-JHM N gene with that of MHV-A59 is attenuating (Cowley et al., 2010). The rA59/N_{JHM} induced a faster spread of virus in the CNS than rA59, whereas the rJHM/N_{A59} demonstrated a restrained viral spread as compare to rJHM. These data illustrated that the N background determined viral spread, which is a constituent of virulence. The N_{JHM} is suspected to be associated to microtubules (Pasick et al., 1994) and then to be able to increase the transport of virus along axons to favor viral spread between neurons to other neurons. Unfortunately, the infection of primary hippocampal neuronal cultures by rA59/N_{JHM} did not demonstrate an increased spread of virus as compared to rA59 (Cowley et al., 2010). Moreover, the N gene influences T-cell infiltration into the brain, as $CD4^+$ and $CD8^+$ T cell response is strong if the virus possesses N_{A59} and weak with the N_{JHM} (Cowley et al., 2010).

2.2.3 Hemagglutinin Esterase glycoprotein (HE)

The hemagglutinin esterase (HE), is an envelope glycoprotein, which is present in some strains of the betacoronaviruses such as the human coronaviruses (HCoV-OC43 and HCoV-HKU1), as well as the bovine coronavirus (BCoV). The JHM strain of MHV expresses the HE glycoprotein, whereas MHV-A59 does not, due to a defective HE gene (Shieh et al.,

1989). Nevertheless, MHV-A59 is able to induce an encephalitis in infected mice but the disease is less important as this strain is less neurovirulent than MHV-JHM. By using targeted RNA recombination to introduce the HE gene of MHV-JHM into the genome of MHV-A59, the role of the HE gene in neurovirulence was addressed. The expression of HE on the MHV-A59 background neither increased virulence in mice (as evaluated by the LD_{50}), nor the production of infectious virus (in brain or liver tissue), or virus spread (revealed by the distribution of viral antigen) (Kazi et al., 2005). Whereas, Kazi and collaborators demonstrated that the expression of HE in combination with the MHV-JHM spike protein in rA59 enhances the disease outcome and increased viral spread in the brain, without changing viral replication, their results suggest that a structurally intact HE, in combination with the MHV-JHM spike protein, has a significant impact on the neurovirulence. In fact, even though the S protein is the main viral factor, which determines tissue tropism and infection of target cell, the HE viral protein appears to serve as a second receptor-binding protein, which increases infection and viral dissemination in the brain (Kazi et al., 2005).

2.3 Human coronaviruses (HCoV)

Human coronaviruses (HCoV) are recognized respiratory pathogens but, in rare cases, they may be associated with encephalitis. As previously mentioned, five different strains of human coronaviruses are currently described: HCoV-OC43, HCoV-229E, HCoV-NL-63, HCoV-HKU1 and SARS-CoV, and neuroinvasive properties were reported for at least three of these five strains. Indeed, our laboratory has demonstrated that HCoV-OC43 and HCoV-229E can infect human neural cells (neurons and glial cells) and does persist in human brains (Bonavia et al., 1997; Arbour et al., 1999a; 1999b; 2000). Others have reported the presence of HCoV-OC43 in a child with acute disseminated encephalomyelitis (Yeh et al., 2004). Moreover, the SARS-CoV epidemics reported in China in the fall of 2002, strongly illustrated the potentially fatal illness caused by a coronavirus (Drosten et al., 2003; Fouchier et al., 2003; Ksiazek et al., 2003). The severe acute respiratory syndrome described was usually transmitted by contact with droplets sprayed into the air by an infected person's coughing. Other symptoms can include high fever, headache, body aches, and pneumonia. A few years after the 2002-2003 epidemics, scientists found that SARS-CoV was able to also infiltrate brain tissue and cause significant CNS problems associated with edema, degeneration of neuronal cells and gliosis, and SARS-CoV RNA could be detected in the brain of patients who died of SARS (Gu et al., 2005; Xu et al., 2005). Moreover, the use of a transgenic mouse model expressing the recognized viral receptor, human angiotensin-converting enzyme 2 (hACE-2), showed that SARS-CoV possesses neuroinvasive properties, as the virus reached the brain by the olfactory bulbs, infecting neuronal cells and induced a lethal disease, with a restrained immune infiltration (Netland et al., 2008).

2.3.1 Animal model to understand the human coronavirus infection

We have characterized the neurotropic, neuroinvasive and neurovirulent properties of HCoV-OC43 through the development of an experimental animal model. We have reported that intranasal (IN) infection of mice with HCoV-OC43 led to acute encephalitis and to a generalized infection of the whole CNS, demonstrating HCoV-OC43 neuroinvasiveness and neurovirulence (Jacomy & Talbot, 2003). Damage to the CNS appeared to be mainly a consequence of direct virus-mediated neuronal injury. Indeed, as illustrated in Figure 1, this acute infection targeted neurons, which underwent vacuolation and degeneration. We were also able to demonstrate that caspase-related virus-induced apoptosis of neuronal cells both

in vitro and *in vivo* (Jacomy and Talbot, 2006). This type of virus-induced apoptosis is of particular interest as in the human brain, activation of caspase 3 is involved in pathologic pathway of influenza encephalopathy (Nakai et al., 2003), reovirus-induced encephalitis (Beckham et al., 2010) and Japanese-encephalitis virus-induced pathology (Yang et al., 2009).

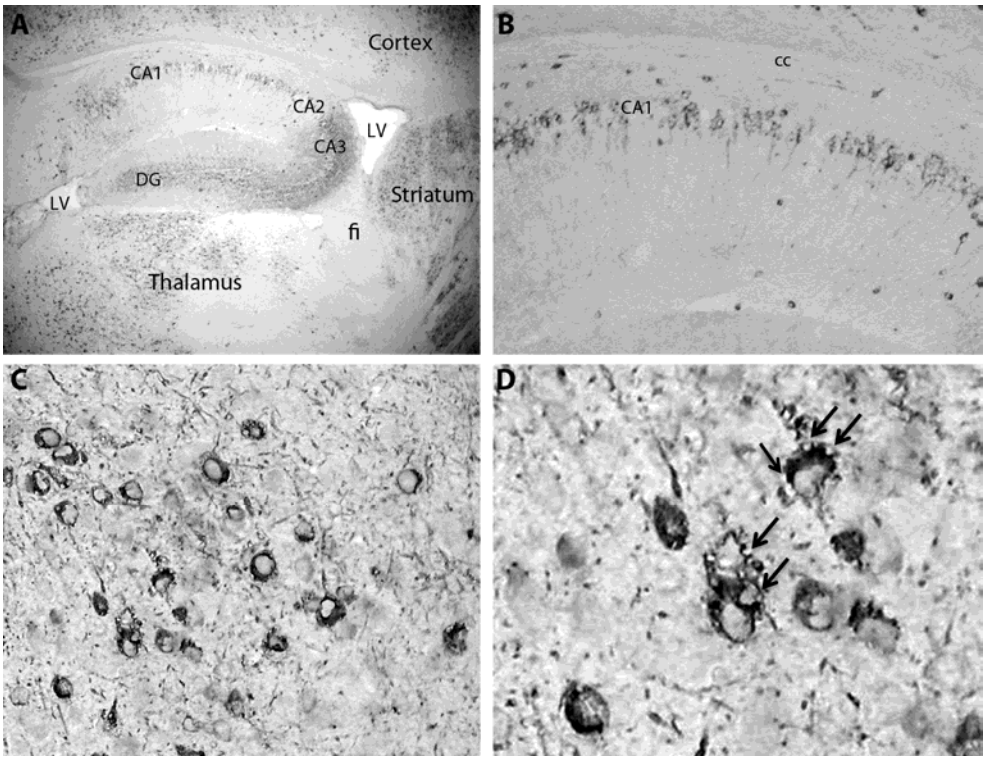

Fig. 1. Infection of neuronal cells by HCoV-OC43. (A) Numerous cells positive for virus antigens at 7 days post-infection (DPI) in the CNS. Virus was present in hippocampal region (especially in pyramidal cell layers CA1, CA2 and CA3, as well as in dentate gyrus (DG)), in cortical area (Cortex), in Striatum as well as in Thalamus. (B) Magnification of pyramidal cell layers CA1, illustrating numerous infected cells stained in black. (C) Infected neurons in the Striatum, at higher magnification (D), numerous vacuolation were present in the cytoplasm of infected neurons (arrows). LV: Lateral ventricle; cc: corpus callosum; fi: fimbria of hippocampus.

While neurons are the primary target of HCoV-OC43, infected regions presented strong microglial reactivity and inflammatory reactions (neuroinflammation). Although initiation of immune responses by microglial cells is normally an important protective mechanism in the CNS, unrestrained inflammatory responses may result in irreversible brain damage. It is likely that strong microglial activation can trigger bystander damage, as they can release large amounts of cytokines and chemokines. In fact, we have recently shown that infection of susceptible mice by HCoV-OC43 induced the production of high level of numerous pro-inflammatory cytokines such as tumor necrosing factor (TNF)-alpha, interleukin (IL)-1 beta

and IL-6, released in the CNS, as well as chemokines and strong infiltration of immune cells (Jacomy et al., 2010). This is again of particular interest since accumulating evidence show that these types of factors may influence the degree of encephalitis. For instance, the mortality rate following JEV encephalitis is directly linked to the concentration of cytokine in serum and cerebrospinal fluid (CSF) in patients (Winter et al., 2004). Furthermore, neuronal cell death in a mice model of Japanese Encephalitis Virus (JEV) infection was demonstrated to be related to the activation of microglia and subsequent production of multiple proinflammatory mediators (Ghoshal et al., 2007). We also reported that apoptosis of neurons occurred in infected and non-infected cells, suggesting that it is independent of the presence of virus (Jacomy et al., 2006). Host adaptive immune response was demonstrated to contribute to HCoV-OC43-induced encephalitis (Butler et al., 2006). We also reported that mice surviving encephalitis developed motor dysfunctions as the result of viral persistence in the CNS (Jacomy et al., 2006). In addition to the direct effect of the viral pathogen, acute encephalopathy may be associated with viral infections and increased plasma concentrations of CXCL8/IL-8 and CCL2/MCP-1, CXCL10/IP-10 and IL-6, without viral neuroinvasion (hyperactivated cytokine/chemokine response) as demonstrated following infection by another respiratory virus, Influenza virus, which can cause encephalitis (Lee et al., 2010). JEV also induces a rapid inflammatory response, which is accompanied by an increased level of cytokines and chemokines in the serum and cerebrospinal fluid of infected patients. Moreover, levels of interferon (IFN)-alpha, TNF-alpha, and the cytokines IL-8 and IL-6 have been associated with a bad outcome (Burke & Morill, 1987; Singh et al., 2000, Winter et al., 2004)

Excitotoxic neurotransmission, which is an excessive stimulation by the neurotransmitter glutamate on its specific receptors (AMPAr and NMDAr), seems to play an important role in neuronal damage during encephalitis as concentration of glutamate in CSF is significantly increased in acute encephalitis (Launes et al., 1998). Moreover, the concentration of glutamate was also correlated with a poor outcome during encephalitis in humans, as well as in an animal model of human encephalitis (Carmen et al., 2009; Launes et al., 1998). During the HCoV-OC43-induced encephalitis, we recently found that hippocampal neurons died in part by this pathological process (Brison et al., submitted for publication). Indeed, treatment of infected mice with the AMPA receptor antagonist (GYKI-52466) did not affect the survival rate of mice but histological analysis revealed that mice treated by the GYKI-52466 presented less neurodegeneration compared to infected mice without the AMPA antagonist, as determined by Neurosilver staining (Figure 2) (Brison et al., submitted for publication). Again, this is of particular interest since glutamate excitotoxicity was demonstrated to be involved in several viral infection such as West Nile virus, Sindbis virus, JEV, HIV and HSV (Blakely et al., 2009; Golembewski et al., 2007; Haughey et al., 2001; Mishra et al., 2007; Nargi-Aizenman et al., 2004). The loss of neuronal subpopulations in the brain during HIV dementia was also related to an indirect mechanism conjugating glial activation, cytokines released and excitotoxic transmission (Alirezaei et al., 2008; Masliah & Mucke, 1996).

We have also demonstrated that the severity of the HCoV-OC43 induced-encephalitis depended on a number of factors such as the genetic background (Jacomy & Talbot, 2003) and the gender of the mice, as revealed by inoculation of male and female animals of different mouse strains, aged 21 days post-natal (DPN). At the equal infectious viral dose, male animals are more susceptible than female animals. For all strains of mice tested, male animals appeared more susceptible than female animals to encephalitis, as illustrated for strains C57BL/6 and BALB/c in Figure 3.

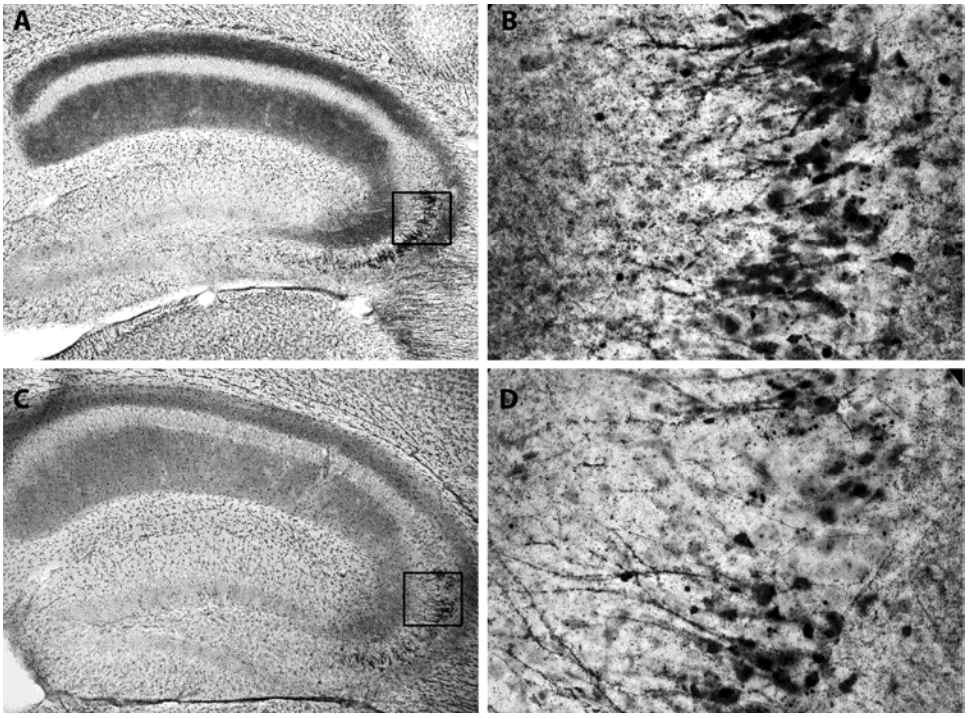

Fig. 2. Hippocampus of mice following HCoV-OC43 infection treated or not treated by the GYKI-52466 antagonist. Following infection, neurodegeneration was investigated with Silver staining in non-treated (A and higher magnification B) and AMPA receptor antagonist-treated mice (C and higher magnification D). Neurons that underwent degeneration appear in black. As illustrated at higher magnification, non-treated mice present more numerous dark CA3 neurons (B) as compared to mice treated with GYKI-52466 (D).

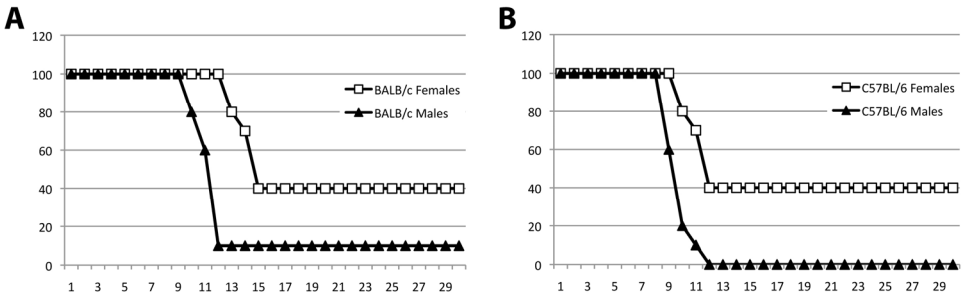

Fig. 3. Survival rate of female versus male mice to a same infectious dose. Mice were monitored for 30 days for mortality following intracerebral infection. C57BL/6 (A) and BALB/c (B) mice were infected, respectively, with $10^{2.5}$ $TCID_{50}$ or $10^{0.5}$ $TCID_{50}$ of virus. For the same infectious dose, male mice were more susceptible to viral infection than female.

How immunological, hormonal, and or genetic differences between males and females could affect gender differences in susceptibility to infection? Males and females are differentially susceptible to several pathogens including viruses (Fish, 2008; Klein, 2000). In fact, in the case of viral infection in general, this difference in susceptibility between males and females was shown for different viruses including Seoul Virus (Klein et al., 2000), and Influenza virus (Avitsur et al., 2011) and this is also true in the particular case of viral infection of the CNS, which leads to encephalitis, for other viruses such as HIV-1 (Wilson et al., 2006), and vesicular stomatitis virus (VSV) (Barna et al., 1996). The concept of sex-based (or gender-based) differences in host response to infection has been studied for many years and appears to be highly related to differences in immunological capacities between males and females (Purtilo & Sullivan, 1979; Fish, 2008). Furthermore, it appears now that even though the relative importance of different factors may vary with the type of infection, X-linked genes, hormones, immunity and, at least in humans, societal context are among the factors that explain this sex-based difference (Fish, 2008; Klein, 2000). Even though it remains difficult to clarify evidence on how the different factors make a difference between genders, studies aimed to addressing the question appear to more and more link specific hormones such as androgens in males and estrogens in females (Klein, 2000; Wilson et al., 2006), host innate immunity (expression of cytokines and of pattern recognition receptors such as toll-like receptors (TLR)) (Hannah et al., 2008; Hill et al., 1998) as well as acquired immunity involving T and B lymphocytes (reviewed in Klein, 2000) to explain part of the puzzle.

As already published in our model, C57BL/6 were more susceptible than BALB/c mice and CD1 mice were in between, being more resistant than C57BL/6 mice and more susceptible than BALB/c mice. As already described, susceptibility to intracellular pathogens depends on human genetics (for review, see Vannberg et al., 2011). Therefore, susceptibility to infectious diseases could be linked to loci or alleles that could favor clearance of virus, such as for hepatitis C virus (Ge et al., 2009; Thomas et al., 2009). In the contrary, genetics may determine persistence of infection, such as in the case of Hepatitis B virus (Kamatani et al., 2009) or restrict viral loads as shown in HIV-1 infections (Fellay et al., 2007; 2009) Furthermore, we also showed that susceptibility to intranasal infection diminished with age (Figure 4), as adult mice became resistant to intranasal infection. All infected mice (21 days post natal (DPN) and more) survived to intranasal infection, no infectious virus was detected in the brain even though viral RNA could be detected in the CNS, demonstrating neuroinvasive properties without evident signs of pathology. This is an interesting fact considering that this restrictive susceptibility to CNS infection and encephalitis appear to exist in humans, where mostly children, the elderly and immuno-compromised individuals are more susceptible (Schneider & Higgs, 2008; Wang et al., 2010).

We also reported that mice became less susceptible to intracerebral infection with the age of mice, as illustrated in Figure 5.

2.4 Other non human coronaviruses as encephalitis-inducing agents

Over the years, some coronaviruses, which can infect cattle or domestic animals, were described as agent able to induced encephalitis in certain conditions.

2.4.1 Swine coronaviruses (HEV)

Hemagglutinating encephalitis virus (HEV) was demonstrated to induce disease ranging from gastroenteritis to encephalomyelitis in piglets (Andries & Pensaert, 1980; Siddell et al.,

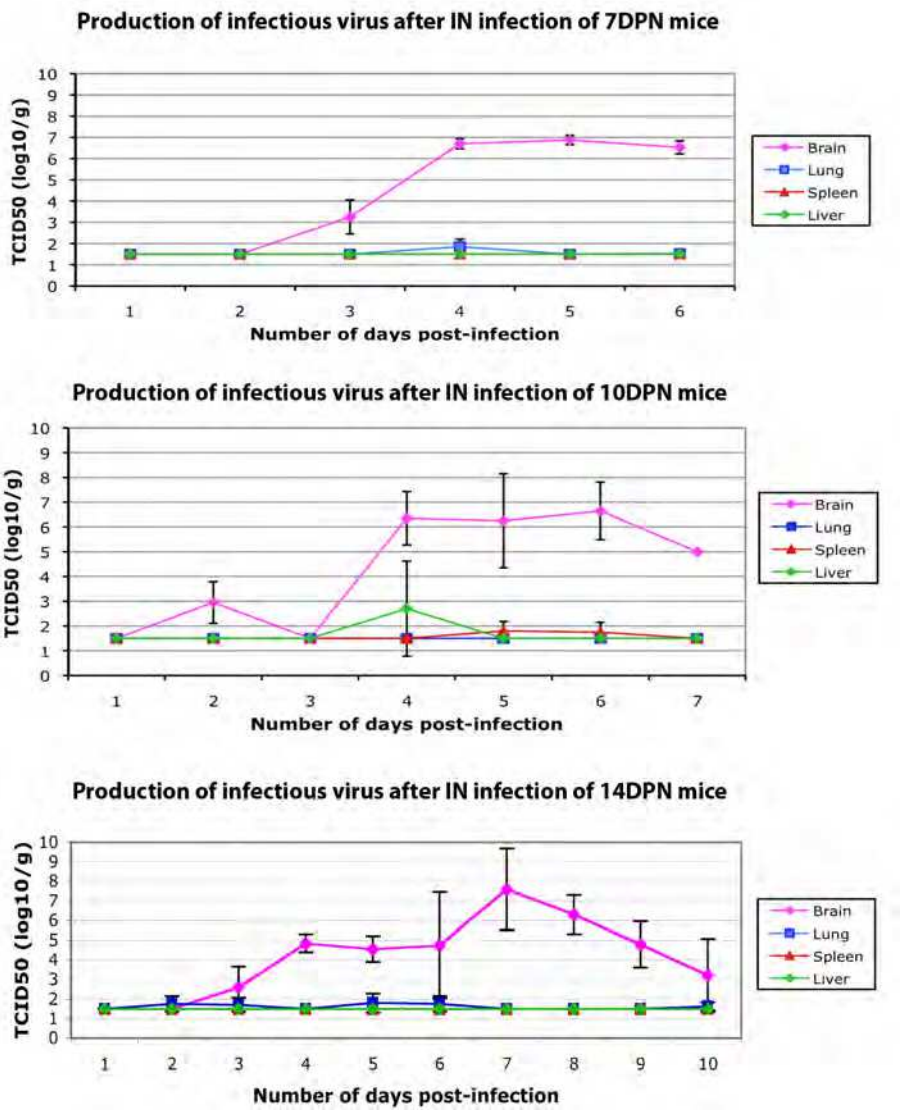

Fig. 4. Neuroinvasive properties following intranasal (IN) inoculation of C57BL/6 aged from 7 to 14 DPN. After inhalation of virus (5000 $TCID_{50}$), 5 mice of each age were sacrificed every 24 hours and the production of infectious virus (virus titers) measured in the CNS, lung, liver and spleen. A detectable level of HCoV-OC43 was found in the brain as early as 2 or 3 DPI (days post-infection), and reached its maximum level a few days later. Infectious virus was occasionally found in lung, spleen or liver (detection limit of the assay: $10^{1.5}$ $TCID_{50}$), especially at times when brain viral titers reached a maximum. Moreover, 7 and 10 DPN mice did not survive HCoV-OC43 inhalation and about 10% of 14 DPN mice did survive.

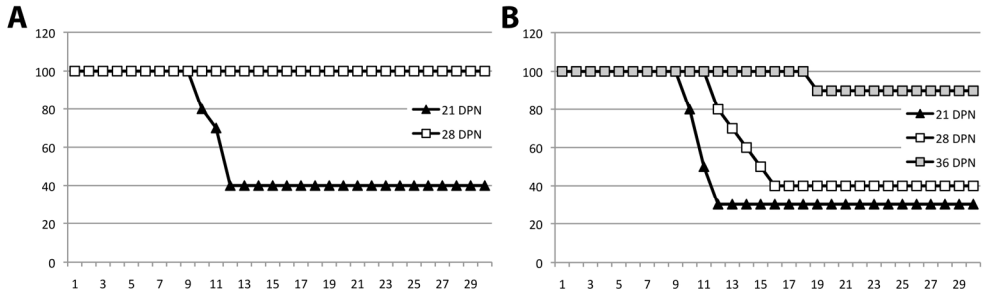

Fig. 5. Susceptibility of mice to the same infectious dose depends of age. (A) C57BL/6 mice became totally unsusceptible to a $10^{0.5}$ infectious dose at 28 days post-natal (DPN), whereas, 60% died following the same infectious dose when they were aged 21 DPN. (B) In the same manner, the susceptibility of CD1 mice to a $10^{1.5}$ infectious doses depended on the age at the time of infection.

1983). The virus was isolated from the brains of suckling pigs suffering from encephalomyelitis several years ago (Greig et al., 1962). The disease could be reproduced experimentally in piglets following intranasal inoculation (Alexander, 1962). A murine model demonstrated that this virus, as other coronaviruses including the HCoV-OC43, is neuroinvasive and neurotropic. In that latter case, neuroinvasion depends on a number of variables such as the route of inoculation and the age of the mice (Yagami et al., 1986; Hirano et al., 1990; 2004). As for the SARS-CoV in mice, HEV induced a poor inflammatory reaction in CNS (Hirano et al., 2004) and unlike HCoV-OC43-infected neurons (Jacomy & Talbot, 2003), HEV-infected cells showed no cytopathological changes.

2.4.2 Feline coronaviruses (FCoV)

Feline infectious peritonitis (FIP) is a common cause of death in cats, caused by a virulent feline coronavirus (FCoV). The virulent form of FCoV, called FIPV, occurs following mutations acquired during a persistent infection (Brown et al., 2009; Rottier et al., 2005; Vennema et al., 1998) and neurologic involvement could occur in FIP disease (Foley et al., 1998; Summers et al., 1995). The colon was identified as the major site of FCoV persistence; nevertheless the virus could also persist in tissue macrophages representing a source for viremia (Kipar et al., 2010). Infected macrophages disseminate systemically and trigger immunological responses resulting in microgranuloma formation, vasculitis, organ failure, and death (Pedersen and Boyle, 1980; Poland et al., 1996 and Vennema et al., 1998). The immunopathogenesis of the disease is poorly understood and often there is little coronavirus present in FIP-affected brain tissue (Foley et al 1998), even though infected phagocytes cells were recovered in CNS of cats (Poncelet et al., 2008), yet inflammatory cells are recruited to the brain and appear to contribute to disease, in part, through secretion of cytokines (Foley et al., 2003).

3. Conclusion

Knowledge of mechanisms and consequences of virus interactions with the nervous system is essential to better understand potentially pathological relevant consequences and design intervention strategies that are highly appropriate to encephalitis. Therefore, collecting new

data will be instrumental to our understanding of how a ubiquitous respiratory virus, the human coronavirus, given the proper susceptibility conditions and proper virus evolution and infection conditions, could trigger the neuropathology that is characteristic of at least some forms of encephalitis.

4. Acknowledgment

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5. References

Alexander, T.J.L. (1962) Viral encephalomyelitis of swine in Ontario. Experimental and natural transmission. Amer. J. Vet. Res. 32, 756–762.

Alirezaei, M., Kiosses, W.B. & Fox, H.S. (2008) Decreased neuronal autophagy in HIV dementia: a mechanism of indirect neurotoxicity. Autophagy 4, 963-966.

Andries, K. & Pensaert, M. (1980) Virus isolation and immunofluorescence in different organs of pigs infected with hemagglutinating encephalomyelitis virus. Amer. J. Vet. Res. 41, 215–218.

Arbour, N., Côté, G., Lachance, C., Tardieu, M., Cashman, N.R. & Talbot, P.J (1999a) Acute and persistent infection of human neural cell lines by human coronavirus OC43. J. Virol. 73, 3338-3350.

Arbour, N., Ekandé, S., Côté, G., Lachance, C., Chagnon, F., Tardieu, M., Cashman, N.R. & Talbot, P.J. (1999b) Persistent infection of human oligodendrocytic and neuroglial cell lines by human coronavirus 229E. J. Virol. 74, 3326-3337.

Arbour, N., Day, R., Newcombe, J. & Talbot, P.J. (2000) Neuroinvasion by human respiratory coronaviruses and association with multiple sclerosis. J. Virol. 74, 8913-8921.

Avitsur, R., Mays, J.W. & Sheridan, J.F. (2011) Sex differences in the response to influenza virus infection: modulation by stress. Horm. Behav. 59, 257-264.

Baric, R.S., Nelson, G.W., Fleming, J.O., Deans, R.J., Keck, J.G., Casteel, N. & Stohlman, S.A. (1988) Interactions between coronavirus nucleocapsid protein and viral RNAs: implications for viral transcription. J. Virol. 62, 4280-4287.

Barna, M., Komatsu, T., Bi, Z. & Reiss, C.S. (1996) Sex differences in susceptibility to viral infection of the central nervous system. J. Neuroimmunol. 67, 31-39.

Beckham, J.D., Tuttle, K.D. & Tyler, K.L. (2010) Caspase-3 activation is required for reovirus-induced encephalitis in vivo. J. Neurovirol. 16, 306-317.

Bender, S.J. & Weiss, S.R. (2010) Pathogenesis of murine coronavirus in the central nervous system. J Neuroimmune Pharmacol. 5, 336-354.

Blakely, P.K., Kleinschmidt-DeMasters, B.K., Tyler, K.L. & Irani, D.N. (2009) Disrupted glutamate transporter expression in the spinal cord with acute flaccid paralysis caused by West Nile virus infection. J. Neuropathol. Exp. Neurol. 68, 1061-1072.

Bonavia, A., Arbour, N., Wee Yong, V. & Talbot, P.J. (1997) Infection of primary cultures of human neural cells by human coronavirus 229E and OC43. J.Virol. 71, 800-806.

Brown, M. A., Troyer, J. L., Pecon-Slattery, J., Roelke, M. E. & O'Brien, S. J. (2009). Genetics and pathogenesis of feline infectious peritonitis virus. Emerg. Infect. Dis. 15, 1445–1452.

Butler, N., Pewe, L., Trandem, K. & Perlman, S. (2006) Murine encephalitis caused by HCoV-OC43, a human coronavirus with broad species specificity, is partly immune-mediated. Virology 347, 410-421.

Burke, D.S. & Morill, J.C. (1987) Levels of interferon in the plasma and cerebrospinal fluid of patients with acute Japanese encephalitis. J. Infect. Dis. 155, 797-799.

Carmen, J., Rothstein, J.D. & Kerr, D.A. (2009) Tumor necrosis factor-alpha modulates glutamate transport in the CNS and is a critical determinant of outcome from viral encephalomyelitis. Brain Res. 1263, 143-154.

Collins, A.R., Knobler, R.L., Powell, H. & Buchmeier, M.J. (1982) Monoclonal antibodies to murine hepatitis virus-4 (strain JHM) define the viral glycoprotein responsible for attachment and cell--cell fusion. Virology 119, 358-371.

Cowley, T.J., Long, S.Y. & Weiss, S.R. (2010) The murine coronavirus nucleocapsid gene is a determinant of virulence. J. Virol. 84, 1752-1763.

de Haan, C.A.M. & Rottier, P.J.M. (2005) Molecular interactions in the assembly of coronaviruses. Adv. Virus Res. 64, 165-230.

Drosten, C., Günther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., Rabenau, H., Panning, M., Kolesnikova, L., Fouchier, R.A., Berger, A., Burguière, A.M., Cinatl, J., Eickmann, M., Escriou, N., Grywna, K., Kramme, S., Manuguerra, J.C., Müller, S., Rickerts, V., Stürmer, M., Vieth, S., Klenk, H.D., Osterhaus, A.D., Schmitz, H. & Doerr, H.W. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N. Engl. J. Med. 348, 1967-1976.

Dubois-Dalcq, M.E., Doller, E.W., Haspel, M.V., & Holmes, K.V. (1982). Cell tropism and expression ofmouse hepatitis viruses (MHV) in mouse spinal cord cultures. Virology 119, 317–331.

Fellay, J., Shianna, K.V., Ge, D., Colombo, S., Ledergerber, B., Weale, M., Zhang, K., Gumbs, C., Castagna, A., Cossarizza, A., Cozzi-Lepri, A., De Luca, A., Easterbrook, P., Francioli, P., Mallal, S., Martinez-Picado, J., Miro, J.M., Obel, N., Smith, J.P., Wyniger, J., Descombes, P., Antonarakis, S.E., Letvin, N.L., McMichael, A.J., Haynes, B.F., Telenti, A., & Goldstein, D.B. (2007) A whole-genome association study of major determinants for host control of HIV-1. Science 317, 944-947.

Fellay, J., Ge, D., Shianna, K.V., Colombo, S., Ledergerber, B., Cirulli, E.T., Urban, T.J., Zhang, K., Gumbs, C.E., Smith, J.P., Castagna, A., Cozzi-Lepri, A., De Luca, A., Easterbrook, P., Günthard, H.F., Mallal, S., Mussini, C., Dalmau, J., Martinez-Picado, J., Miro, J.M., Obel, N., Wolinsky, S.M., Martinson, J.J., Detels, R., Margolick, J.B., Jacobson, L.P., Descombes, P., Antonarakis, S.E., Beckmann, J.S., O'Brien, S.J., Letvin, N.L., McMichael, A.J., Haynes, B.F., Carrington, M., Feng, S., Telenti, A., Goldstein, D.B.& NIAID Center for HIV/AIDS Vaccine Immunology (CHAVI). (2009) Common genetic variation and the control of HIV-1 in humans. PLoS Genet. 5, e1000791.

Fish, E.N. (2008) The X-files in immunity: sex-based differences predispose immune responses. Nat. Rev. Immunol. 8, 737-744.

Foley, J., Lapointe, J.-M., Koblik, P., Poland, A. & Pedersen, N. 1998. Diagnostic features of neurologic feline infectious peritonitis. J. Vet. Int. Med. 12, 36–63.

Foley, J.E., Rand, C. & Leutenegger, C. (2003) Inflammation and changes in cytokine levels in neurological feline infectious peritonitis. J. Feline Med. Surg. 5, 313-322.

Fouchier, R.A., Kuiken, T., Schutten, M., van Amerongen, G., van Doornum, G.J., van den Hoogen, B.G., Peiris, M., Lim, W., Stöhr, K. & Osterhaus, A.D. (2003) Aetiology: Koch's postulates fulfilled for SARS virus. Nature 423, 240.

Gallagher, T.M., Parker, S.E. & Buchmeier, M.J. (1990) Neutralization-resistant variants of a neurotropic coronavirus are generated by deletions within the amino-terminal half of the spike glycoprotein. J. Virol. 64, 731-741.

Ge, D., Fellay, J., Thompson, A.J., Simon, J.S., Shianna, K.V., Urban, T.J., Heinzen, E.L., Qiu, P., Bertelsen, A.H., Muir, A.J., Sulkowski, M., McHutchison, J.G. & Goldstein, D.B. (2009) Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 461, 399-401.

Ghoshal, A., Das, S., Ghosh, S., Mishra, M.K., Sharma, V., Koli, P., Sen, E. & Basu, A. (2007) Proinflammatory mediators released by activated microglia induces neuronal death in Japanese encephalitis. Glia 55, 483-496.

Golembewski, E.K., Wales, S.Q., Aurelian, L. & Yarowsky, P.J. (2007) The HSV-2 protein ICP10PK prevents neuronal apoptosis and loss of function in an in vivo model of neurodegeneration associated with glutamate excitotoxicity. Exp. Neurol. 203, 381-393.

Greig, A.S., Mitchell, D., Cormer, A.H., Bannister, G.L., Meads, E.B. & Julian, R.J. (1962) Hemagglutinating virus producing encephalomyelitis in baby pigs. Can J Comp Med. Vet. Sci. 26, 49-56.

Gu, J., Gong, E., Zhang, B., Zheng, J., Gao, Z., Zhong, Y., Zou, W., Zhan, J,. Wang, S., Xie, Z., Zhuang, H., Wu, B., Zhong, H., Shao, H., Fang, W., Gao, D., Pei, F., Li, X., He, Z., Xu, D., Shi, X., Anderson, V.M. & Leong, A.S. (2005) Multiple organ infection and the pathogenesis of SARS. J. Exp. Med. 202, 415-424.

Hannah, M.F., Bajic, V.B. & Klein, S.L. (2008) Sex differences in the recognition of and innate antiviral responses to Seoul virus in Norway rats. Brain Behav. Immun. 22, 503-516.

Haughey, N.J., Nath, A., Mattson, M.P., Slevin, J.T. & Geiger, J.D. (2001) HIV-1 Tat through phosphorylation of NMDA receptors potentiates glutamate excitotoxicity. J. Neurochem. 78, 457-467.

Hill, K.E., Pigmans, M., Fujinami, R.S. & Rose, J.W. (1998) Gender variations in early Theiler's virus induced demyelinating disease: differential susceptibility and effects of IL-4, IL-10 and combined IL-4 with IL-10. J. Neuroimmunol. 85, 44-51.

Hirano, K., Ona, T., Takasawa, T., Murakami & Haga, S. (1990) Replication and plaque formation of swine hemagglutinating encephalomyelitis virus (67N) in swine cell line, SK-K culture. J. Virol. Methods 27, 91–100.

Hirano, N., Nomura, R., Tawara, T. & Tohyama, K. (2004) Neurotropism of swine haemagglutinating encephalomyelitis virus (coronavirus) in mice depending upon host age and route of infection. J. Comp. Pathol. 130, 58-65.

Iacono, K. T., L. Kazi, & Weiss, S.R. (2006) Both spike and background genes contribute to murine coronavirus neurovirulence. J. Virol. 80, 6834–6843.

Jacomy, H. & Talbot, P.J. 2003. Vacuolating encephalitis in mice infected by human coronavirus OC43. Virology 315, 20-33.

Jacomy, H., Fragoso, G., Almazan, G., Mushynski, W.E. & Talbot, P.J. (2006) Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/c mice. Virology 349, 335-346.

Jacomy, H. & Talbot, P.J. (2006) HCoV-OC43-induced apoptosis of murine neuronal cells. Adv. Exp. Med. Biol. 581, 473-478.

Jacomy, H., St-Jean, J.R., Brison, E., Marceau, G., Desforges, M. & Talbot, P.J. (2010) Mutations in the spike glycoprotein of human coronavirus OC43 modulate disease in BALB/c mice from encephalitis to flaccid paralysis and demyelination. J. Neurovirol. 16, 279-293.

Kamatani, Y., Wattanapokayakit, S., Ochi, H., Kawaguchi, T., Takahashi, A., Hosono, N., Kubo, M., Tsunoda, T., Kamatani, N., Kumada, H., Puseenam, A., Sura, T., Daigo, Y., Chayama, K., Chantratita, W., Nakamura, Y. & Matsuda, K. (2009) A genome-wide association study identifies variants in the HLA-DP locus associated with chronic hepatitis B in Asians. Nat. Genet. 41, 591-595.

Kazi, L., Lissenberg, A., Watson, R., de Groot, R.J. & Weiss, S.R. (2005) Expression of hemagglutinin esterase protein from recombinant mouse hepatitis virus enhances neurovirulence. J. Virol. 79, 15064-15073.

Kipar, A., Meli, M.L., Baptiste, K.E., Bowker, L.J. & Lutz, H. (2010) Sites of feline coronavirus persistence in healthy cats. J. Gen. Virol. 91, 1698-1707.

Klein S.L. (2000) The effects of hormones on sex differences in infection: from genes to behavior. Neurosci. Biobehav. Rev. 24, 627-638.

Ksiazek, T.G., Erdman, D., Goldsmith, C.S., Zaki, S.R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J.A., Lim, W., Rollin, P.E., Dowell, S.F., Ling, A.E., Humphrey, C.D., Shieh, W.J., Guarner, J., Paddock, C.D., Rota, P., Fields, B., DeRisi, J., Yang, J.Y., Cox, N., Hughes, J.M., LeDuc, J.W., Bellini, W.J., Anderson, L.J. & SARS Working Group. (2003). A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med. 348:1953-1966.

Lane, T.E. & Hosking, M.P. (2010) The pathogenesis of murine coronavirus infection of the central nervous system. Crit. Rev. Immunol. 30:119-130.

Launes, J., Sirén, J., Viinikka, L., Hokkanen, L. & Lindsberg, P.J. (1998) Does glutamate mediate brain damage in acute encephalitis? Neuroreport 9, 577-581.

Lee, N., Wong, C.K., Chan, P.K., Lindegardh, N., White, N.J., Hayden, F.G., Wong, E.H., Wong, K.S., Cockram, C.S., Sung, J.J. & Hui, D.S. (2010) Acute encephalopathy associated with influenza A infection in adults. Emerg. Infect. Dis. 16, 139-142.

MacNamara, K.C., Chua, M.M., Nelson, P.T., Shen, H., & Weiss, S.R. (2005) Increased epitope-specific CD8+ T cells prevent murine coronavirus spread to the spinal cord and subsequent demyelination. J. Virol. 79, 3370-3381.

MacNamara, K.C., Bender, S.J., Chua,M.M., Watson, R. & Weiss, S.R. (2008) Priming of CD8 T cells during central nervous system infection with a murine coronavirus is strain-dependent. J. Virol. 82, 6150–6160.

Masliah, E., Ge, N. & Mucke, L. (1996) Pathogenesis of HIV-1 associated neurodegeneration. Crit. Rev. Neurobiol. 10, 57-67.

Masters, P. S. (2006) The molecular biology of coronaviruses. Adv. Virus Res. 66, 193-292.

Maurizi, C.P., (2010) Influenza caused epidemic encephalitis (encephalitis lethargica): the circumstantial evidence and a challenge to the nonbelievers. Med. Hypotheses. 74, 798-801.

Mishra, M.K., Koli, P., Bhowmick, S. & Basu, A. (2007) Neuroprotection conferred by astrocytes is insufficient to protect animals from succumbing to Japanese encephalitis. Neurochem Int. 50, 764-773.

Miura, T.A., Travanty, E.A., Oko, L., Bielefeldt-Ohmann, H., Weiss, S.R., Beauchemin, N. & Holmes, K.V. (2008) The spike glycoprotein of murine coronavirus MHV-JHM mediates receptor-independent infection and spread in the central nervous system of Ceacam1a-/- mice. J. Virol. 82, 755–763.

Nakai, Y., Itoh, M., Mizuguchi, M., Ozawa, H., Okazaki, E., Kobayashi, Y., Takahashi, M., Ohtani, K., Ogawa, A., Narita, M., Togashi, T. & Takashima, S. (2003) Apoptosis and microglial activation in influenza encephalopathy. Acta Neuropathol. 105, 233-239.

Nargi-Aizenman, J.L., Havert, M.B., Zhang, M., Irani, D.N., Rothstein, J.D. & Griffin, D.E. (2004) Glutamate receptor antagonists protect from virus-induced neural degeneration. Ann. Neurol. 55, 541-549.

Netland, J., Meyerholz, D.K., Moore, S., Cassell, M. & Perlman, S. (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J. Virol. 82, 7264-7275.

Pasick, J.M., Kalicharran, K. & Dales, S. (1994) Distribution and trafficking of JHM coronavirus structural proteins and virions in primary neurons and the OBL-21 neuronal cell line. J. Virol. 68, 2915-2928.

Pedersen, N. & Boyle, J. (1980) Immunologic phenomena in the effusive form of feline infectious peritonitis. Amer. J. Vet. Res. 41, 868–876.

Phillips, J.J., Chua, M.M., Lavi, E., & Weiss, S.R. (1999) Pathogenesis of chimeric MHV4/MHV-A59 recombinant viruses: the murine coronavirus spike protein is a major determinant of neurovirulence. J. Virol. 73, 7752-7760.

Phillips, J.J., Chua, M.M., Rall, G.F. & Weiss, S.R. (2002) Murine coronavirus spike glycoprotein mediates degree of viral spread, inflammation, and virus-induced immunopathology in the central nervous system. Virology 301, 109-120.

Poland, A.M., Vennema, H., Foley, J.E. & Pedersen, N.C., (1996) Two related strains of feline infectious peritonitis virus isolated from immunocompromised cats infected with a feline enteric coronavirus. J. Clin. Microbiol. 34, 3180–3184.

Poncelet, L., Coppens, A., Peeters, D., Bianchi, E., Grant, C.K. & Kadhim, H. (2008) Detection of antigenic heterogeneity in feline coronavirus nucleocapsid in feline pyogranulomatous meningoencephalitis. Vet. Pathol. 45, 140-153.

Purtilo, D.T. & Sullivan, J.L. (1979) Immunological bases for superior survival of females. Amer. J. Dis. Child. 133, 1251-1253.

Resta, S., Luby, J.P., Rosenfeld, C.R. & Siegel, J.D. (1985). Isolation and propagation of a human enteric coronavirus. Science 229, 978-981.

Riski, N., & Hovi, T. (1980). Coronavirus infections of man associated with diseases other than the common cold. J. Med. Virol. 6, 259–265.

Rottier, P.J.M., Nakamura, K., Schellen, P., Volders, H. & Haijema, B.J. (2005) Acquisition of macrophage tropism during the pathogenesis of feline infectious peritonitis is determined by mutations in the feline coronavirus spike protein. J. Virol. 79, 14122–14130.

Schneider, B.S. & Higgs, S. (2008) The enhancement of arbovirus transmission and disease by mosquito saliva is associated with modulation of the host immune response. Trans. R. Soc. Trop. Med. Hyg. 102, 400-408.

Shieh, C.K., Lee, H.J., Yokomori, K., La Monica, N., Makino, S. & Lai, M.M. (1989) Identification of a new transcriptional initiation site and the corresponding functional gene 2b in the murine coronavirus RNA genome. J. Virol. 63, 3729–3736.

Siddell, S.G., Anderson, R., Cavanagh, D., Fujiwara, K., Klenk, H.D., Macnaughton, M.R.. Pensaert, M., Stohlman S.A. & van der Zeijist B.A.M. (1983) Coronaviridae. Intervirology 20, 181–189.

Singh, A., Kulshreshtha, R., & Mathur, A. (2000) Secretion of the chemokine interleukin- 8 during Japanese encephalitis virus infection. J. Med. Microbiol. 49, 607-612.

Stohlman, S.A. & Hinton, D.R. (2001) Viral induced demyelination. Brain Pathol. 11, 92-106.

Sturman, L.S., Holmes, K.V. & Behnke, J. (1980) Isolation of coronavirus envelope glycoproteins and interaction with the viral nucleocapsid. J. Virol. 33, 4494-4462.

Summers, B.A., Cummings, J.F. & deLahunta, A. (1995) Inflammatory diseases of the central nervous system. In: *Veterinary Pathology*, Summers, B.A., Cummings, J.F. & deLahunta, A., eds., pp. 95–188. Mosby, St. Louis, MO.

Thomas, D.L., Thio, C.L., Martin, M.P., Qi, Y., Ge, D., O'Huigin, C., Kidd, J., Kidd, K., Khakoo, S.I., Alexander, G., Goedert, J.J., Kirk, G.D., Donfield, S.M., Rosen, H.R., Tobler, L.H., Busch, M.P., McHutchison, J.G., Goldstein, D.B. & Carrington, M. (2009) Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461, 798-801.

Vannberg, F.O., Chapman, S.J. & Hill, A.V.S (2011) Human genetic susceptibility to intracellular pathogens. Immunol. Rev. 240, 105–116.

Vennema, H., Poland, A., Foley, J. & Pedersen, N. C. (1998) Feline infectious peritonitis viruses arise by mutation from endemic feline enteric coronaviruses. Virology 243, 150–157.

Wang, G.F., Li, W. & Li, K. (2010) Acute encephalopathy and encephalitis caused by influenza virus infection. Curr. Opin. Neurol. 23, 305-311.

Wege, H., Winter, J. & Meyermann, R. (1988) The peplomer protein E2 of coronavirus JHM as a determinant of neurovirulence: definition of critical epitopes by variant analysis. J. Gen. Virol. 69, 87-98.

Williams, R.K., Jiang, G.S. & Holmes, K.V. (1991) Receptor for mouse hepatitis virus is a member of the carcinoembryonic antigen family of glycoproteins. Proc. Natl Acad. Sci . U.S.A. 88, 5533-5536.

Wilson, M.E., Dimayuga, F.O., Reed, J.L., Curry, T.E., Anderson, C.F., Nath, A. & Bruce-Keller, A.J. (2006) Immune modulation by estrogens: role in CNS HIV-1 infection. Endocrine 29, 289-297.

Winter, P.M., Dung, N.M., Loan, H.T., Kneen, R., Wills, B., Thu le, T., House, D., White, N.J, Farrar, J.J., Hart, C.A. & Solomon, T. (2004) Proinflammatory cytokines and chemokines in humans with Japanese encephalitis. J. Infect. Dis. 190, 1618–1626.

Wodarz, D., & Krakauer, D.C. (2000). Defining CTL-induced pathology: Implications for HIV. Virology 274, 94–104.

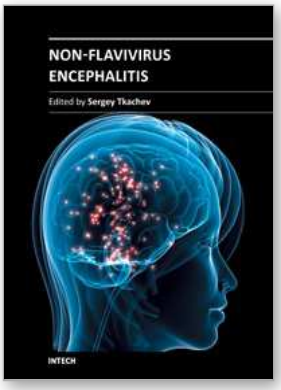
Xu, J., Zhong, S., Liu, J., Li, L., Li, Y., Wu, X., Li, Z., Deng, P., Zhang, J., Zhong, N., Ding, Y. & Jiang, Y. (2005) Detection of severe acute respiratory syndrome coronavirus in the

brain: potential role of the chemokine mig in pathogenesis. Clin. Infect. Dis. 41, 1089-1096.

Yagami, K., Yagami, K., Hirai, K. & Hirano, N. (1986) Pathogenesis of haemagglutinating encephalomyelitis virus (HEV) in mice experimentally infected by different routes. J. Compar. Pathol. 96, 645–657.

Yang, T.C., Shiu, S.L., Chuang, P.H., Lin, Y.J., Wan, L., Lan, Y.C. & Lin, C.W. (2009) Japanese encephalitis virus NS2B-NS3 protease induces caspase 3 activation and mitochondria-mediated apoptosis in human medulloblastoma cells. Virus Res. 143, 77-85.

Yeh, E.A., Collins, A., Cohen, M.E., Duffner, P.K. & Faden, H. (2004) Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics 113, 73-76.



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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