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The Development of Encephalitis Following Tick-Borne Encephalitis Virus Infection in a Mouse Model

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1. Introduction

Tick-borne encephalitis virus (TBEV) belongs to the genus *Flavivirus* in the family *Flaviviridae*. TBEV is transmitted through the bite of an infected tick and causes acute central nervous system (CNS) disease in humans (Dumpis, Crook, and Oksi, 1999; Lindquist and Vapalahti, 2008). TBEV is prevalent over a wide area of Europe and Asia, and is geographically and genetically divided into three subtypes, the European, Siberian and far eastern subtypes (Ecker et al., 1999; Hayasaka et al., 2001b). The endemic areas of Europe and Asia correspond to the geographical distribution of *Ixodes* tick species (Burke and Monath, 2001; Dumpis, Crook, and Oksi, 1999).

Tick-borne encephalitis (TBE) cases exhibit neurological symptoms including fever, headache, meningitis, meningoencephalitis and meningoencephalomyelitis, the latter being evident in the most severe cases (Dumpis, Crook, and Oksi, 1999). These non-specific clinical features of TBE may be due to widespread occurrence of neuronal dysfunction at different sites in the CNS. Hence, laboratory diagnosis is required to distinguish TBE from other neurological disorders (Charrel et al., 2004; Holzmann, 2003).

The laboratory mouse model is commonly employed to elucidate the mechanism of disease development following TBEV infection *in vivo*. The pathogenetic process following experimental infection with TBEV is fundamentally similar to that of other encephalitic flaviviruses including Japanese encephalitis virus (JEV), West Nile virus (WNV) and Murray Valley encephalitis virus (MVEV) (Albrecht, 1968; Burke and Monath, 2001; Garcia-Tapia et al., 2007). In the mouse model, the CNS pathology of TBEV and other encephalitic flaviviruses consists of two distinct features: neuroinvasiveness and neurovirulence. It is generally considered that death following peripheral infection represents neuroinvasiveness, whereas mortality following direct intracerebral infection represents neurovirulence (Mandl, 2005; Monath, 1986).

Recent works have proposed that CNS pathology following TBEV infection is a consequence of viral infection of the corresponding cells and the resulting inflammatory response. Direct viral infection of neurons is considered to be the major cause of neurological disease because viral infections cause apoptosis or degeneration of neurons *in vivo* and *in vitro* (Couderc et al., 2002; Liao et al., 1997; Prikhod'ko et al., 2001; Shrestha, Gottlieb, and Diamond, 2003). In addition, recent studies have demonstrated that immunopathological effects also contribute to the severity of CNS pathology (Hayasaka et al., 2009; Ruzek et al., 2009; Wang et al., 2003).

In this chapter, we discuss the multiple mechanisms of disease development observed in a mouse model following peripheral and intracerebral infection with TBEV.

2. Experimental infection in mice

2.1 Peripheral infection

Peripheral infection such as subcutaneous, foot-pad or intradermal route is considered to be a replica of natural infection resulting from the bite of an infected tick. From studies of encephalitic flavivirus infections, it is believed that initial virus replication occurs in dendritic cells (DCs) such as Langerhans cells at the site of infection, and infected DCs migrate to draining lymph nodes. After viremia and replication in peripheral organs, the virus invades the CNS and the host develops CNS disease, although the mechanism by which the blood-brain-barrier is crossed is not completely understood (Byrne et al., 2001; Dumpis, Crook, and Oksi, 1999; Robertson et al., 2009; Samuel and Diamond, 2006). Thus, peripheral infection is generally regarded as a model for neuroinvasiveness.

Following subcutaneous infection with low challenge dose (10^3 PFU) of TBEV, infectious virus is first detected in peripheral organs such as blood, spleen, thymus, lung (Hayasaka et al., 2009), liver and kidney (Hayasaka et al., unpublished data) at 1 to 3 days post-infection (p.i.), and subsequently appears in the CNS at 5 to 7 days p.i.. However, virus replication in peripheral organs does not appear to correlate with the progression of disease, because mice did not have apparent clinical signs during the peak stages of infectious virus in peripheral organs (Hayasaka et al., 2009).

2.2 Intracerebral infection

Intracerebral infection is commonly performed to examine direct neuronal virulence and pathogenicity in the CNS. Intracerebral infection usually results in high mortality rates, and 50% lethal doses (LD_{50}) are often below 1PFU (Chiba et al., 1999a; Monath et al., 1980). Thus, it is believed that the ensuing intracerebral infection and lethal encephalitis after viral entry into the CNS directly represent neurovirulence.

We previously showed that following intracerebral infection with TBEV, virus replication occurred almost simultaneously in peripheral and CNS organs, and acute viral replication was observed throughout the CNS (Hayasaka et al., 2010). Thus, mortality following intracerebral infection is directly related to the severity of viral infection in the CNS (Hayasaka et al., 2010).

2.3 Virus tropism within CNS

Interestingly, virus tropism has been observed in the CNS following TBEV infection. After subcutaneous infection with low virus challenge doses of TBEV Oshima strain, the brain cortex or cerebellum was infected at early or late stage of infection, respectively (Hayasaka et al., 2009). In particular, disappearance of Purkinje cells was observed at late periods post-infection. On the other hand, subcutaneous infection with high virus challenge doses resulted in acute and widespread neuronal infection without significant differences between the brain cortex, thalamus, cerebellum, brainstem and spinal cord (Hayasaka et al., 2009).

This virus tropism of TBEV within the CNS is clearly distinguished from the tropism of other encephalitic flaviviruses, e.g. JEV infection, in which infectious virus is mainly detected in the brain cortex regardless of inoculation route and challenge dose (Hayasaka, unpublished data).

2.4 Mortality as an index of virulence and pathogenesis

It has been generally accepted that CNS infection causes lethal encephalitis. Thus, death has been used as an index of pathogenesis, and mortality is considered as a measure of neuroinvasiveness or neurovirulence following peripheral or intracerebral infection, respectively. 50% lethal dose (LD_{50}) is often determined to compare the virulence of different virus strains or the pathogenesis in different conditions of infection.

However, the role of neuroinvasiveness in mortality is controversial because some mice recovered from illness with neuropathological sequelae following peripheral infection (Chiba et al., 1999a; Hayasaka et al., 2001b; Hayasaka et al., 1999). Thus, viral neuroinvasion following peripheral infection does not simply determine whether or not the mice will die; rather, mortality is determined after the development of CNS disease. In other words, the mechanism of mortality following peripheral infection differs from that of intracerebral infection.

2.4.1 Dose-independent mortality

LD_{50} is determined based on the correlation of increased challenge doses and increased mortality rates (Reed and Muench, 1938). However, with some strains of encephalitic flavivirus including TBEV, mice do not exhibit a normal dose response curve of mortality following peripheral infection. This phenomenon was first reported in the 1940's (Lennette, 1944), but the reason for these apparent discrepancies is not fully understood.

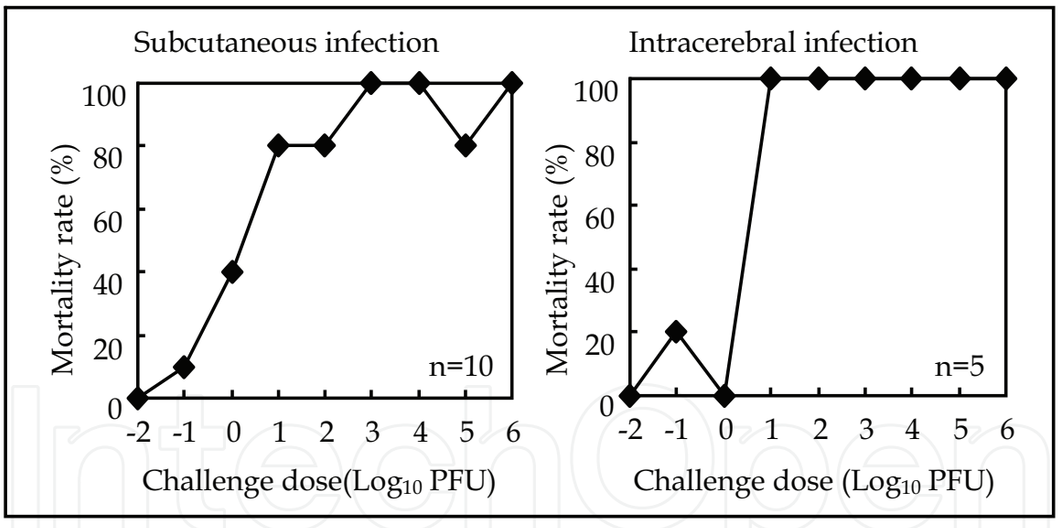

Fig. 1. Mortality rates following subcutaneous and intracerebral inoculation with serial challenge doses of TBEV IR strain

Two patterns of dose-independent mortality are suggested based on our studies. In the first pattern, no increase in mortality rate was observed for low dose challenges, e.g. around 50% mortality between 10^2 to 10^6 PFU inoculations (Hayasaka et al., 2009). This phenomenon was observed following peripheral infection with the Oshima, KH and VL strains (Chiba et al., 1999a; Hayasaka et al., 2001a; Hayasaka et al., 2001b; Hayasaka et al., 1999). All of the mice tested positive for TBEV-specific antibody in those challenge doses, indicating an infectious rate of 100% (Hayasaka, unpublished data). Furthermore, viral load in the CNS was not significantly different between 10^2 to 10^6 PFU challenge doses, and the level of infectious

viruses detected in the CNS of recovering mice were similar to dying mice (Hayasaka et al., 2009). From these observations, we hypothesize that neuroinvasion following peripheral infection does not simply determine mortality, and dose independence is attributable to the outcome of viral infection and host response in peripheral and/or CNS tissues. Thus, elucidation of CNS pathology relating to disease severity and mortality could be an important approach to understand this pattern of dose-independent mortality.

Another pattern of dose-independent mortality is characterized by a reduction in mortality rate (<100%) using challenge doses higher than 100% lethal dose. For example, subcutaneous infection with 10^3 PFU of IR strain induced 100% mortality, but 10^5 PFU challenge dose exhibited 80% mortality rate (Fig. 1). Interestingly, the surviving mice did not have apparent clinical signs such as weight reduction, suggesting that peripheral infection and/or viral invasion in the CNS might not have occurred. We speculate that at early stage of infection, several factors involving innate immunity contribute to this pattern of dose-independent mortality.

2.4.2 Dose-dependent mortality

Dose-dependent mortality, on the other hand, is typically observed in intracerebral infection with any TBEV strain. For example, intracerebral inoculation with the Oshima or IR strain resulted to dose-dependent mortality, with 100% mortality attainable using more than 10^1 PFU (Hayasaka et al., 2010) (Fig. 1).

Furthermore, peripheral infection with some strains such as Sofjin, IR and Hochosterviz showed essentially dose-dependent mortality, and LD_{50} could be determined (Chiba et al., 1999a; Hayasaka et al., 2001a), although some dose-independent mortality was observed in challenge doses higher than 100%lethal dose, as described above (Fig. 1).

3. Two distinct features of early and late mortality

We recently showed that mice died either at early or late stages of infection after peripheral infection with the Oshima strain of TBEV (Hayasaka et al., 2009). Whether mice show early or late mortality is determined by the infectious route, virus strain and inoculation dose. Importantly, dose-dependent or dose-independent mortality is closely associated with early or late mortality, respectively. Thus, in order to understand dose-independent mortality, elucidating the mechanism of late mortality in particular is important.

3.1 Early mortality

3.1.1 Intracerebral inoculation

Intracerebral inoculation of the Oshima strain in mice caused death starting at 7 days p.i., and most died within 10 days p.i. regardless of the challenge dose (Hayasaka et al., 2010). Early death was also observed following intracerebral inoculation with the IR strain (Fig. 2). Infected mice remained asymptomatic for 4 to 5 days, after which they acutely exhibited clinical signs including weight loss, slowness in movement, ataxia, piloerection and anorexia. Mice exhibited neurological signs of paralysis such as rigidity and flaccid paralysis from 7 days p.i., although some mice did not have apparent paralysis before death (Hayasaka et al., 2010). Survivals challenged with less than 10^1 PFU were IgG negative for TBEV antigen, indicating that only positively infected mice eventually die (Hayasaka et al., unpublished data). These results suggest that intracerebral infection directly correlates with mortality, and is characterized by early death.

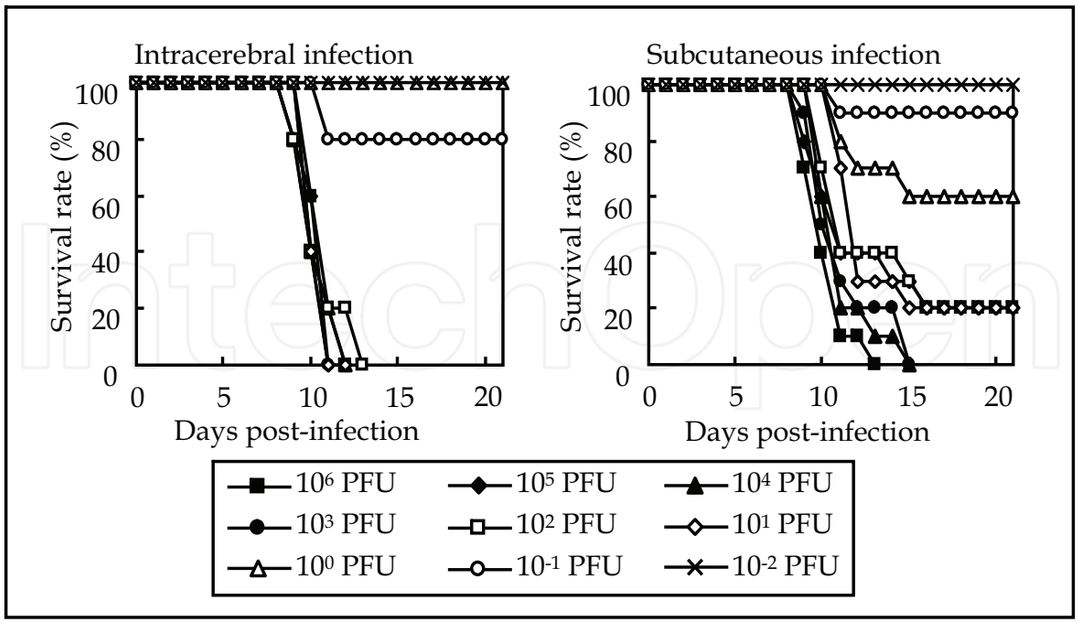

Fig. 2. Daily survival rates following intracerebral and subcutaneous inoculation with serial challenge doses of TBEV IR strain

3.1.2 Peripheral inoculation with highly virulent strains

Following intraperitoneal inoculation with Sofjin and Hochosterwitz strains, which exhibit dose-dependent mortality, mice died early at 8-10 days (Chiba et al., 1999b). Subcutaneous infection with the IR strain also exhibited early death; mice began to die at 8 days p.i., and most died within 11 days p.i. (Fig. 2). These observations suggest that peripheral inoculation with these TBEV strains cause early mortality like intracerebral infection.

3.1.3 Peripheral inoculation with high virus challenge dose

Subcutaneous inoculation with high challenge dose (>10^7 PFU) of the Oshima strain resulted in early mortality at a rate of more than 80% (Hayasaka et al., 2009). Mice started to die at 8 days p.i. and most mice died by 13-14 days p.i.. These infections elicited early onset of weight loss, with acute weight reduction from 5-6 days p.i. (Hayasaka et al., 2009). These observations suggest that high challenge dose of peripheral infection also induce early mortality like intracerebral infection and subcutaneous infection with highly virulent strains.

3.1.4 Severe CNS infection contributes to early mortality

Early mortality strongly correlates with acute and widespread neuronal degeneration due to viral cytopathic effects in the CNS (Hayasaka et al., 2009; Hayasaka et al., 2010). Following intracerebral infection with the Oshima strain, virus replication occurred almost simultaneously in peripheral and CNS organs. At day 6 p.i., viral load was significantly increased to more than 10^8 PFU/g of tissue in all regions of the CNS including the brain cortex, thalamus, cerebellum, brain stem and spinal cord (Hayasaka et al., 2010). Histopathological analysis corresponded well with the viral load, demonstrating acutely necrotic neurons and mild inflammation throughout the CNS, particularly in the brain

cortex, thalamus, cerebellum and lumber spinal cord. All degenerated cells examined were TBEV antigen-positive (Hayasaka et al., 2010).
Subcutaneous infection with a high challenge dose of Oshima strain also showed early CNS infection at 1 day p.i., almost simultaneously with peripheral organ replication (Hayasaka et al., 2009). The viral load peaked in the CNS at 7 days p.i., and mice started to die at around the same period. Consistent with the viral load, histopathological examination showed acute necrotic neurons with TBEV antigens and inflammatory reactions throughout the CNS involving the brain cortex, thalamus, cerebellum, brainstem and spinal cord (Hayasaka et al., 2009). Furthermore, we showed that subcutaneous infection with low challenge dose of the Sofjin and IR strains also exhibited severe CNS infection in mice, indicating that even low dose challenges with these strains rapidly reach a lethal level (Hayasaka et al., unpublished data).
These results strongly suggest that early death primarily results from acute neurological dysfunction throughout the CNS due to viral cytopathic effects, and mice showing clinical signs of illness subsequently die. Thus, CNS pathology is directly linked to lethality, and mortality rate is dose-dependent in TBEV infections with early mortality.

3.2 Late mortality

3.2.1 Peripheral inoculation with low virulent strain

We previously showed that subcutaneous infection with a lower virus challenge dose (10^2 - 10^6 PFU) of the TBEV Oshima strain resulted in 40 to 60% mortality without obvious difference in mortality rates at any of the challenge doses. Mice started to die after 11 days p.i. and the average of survival times were around 15-16 days p.i., irrespective of the challenge dose (Hayasaka et al., 2009).
Interestingly, all low challenge doses (10^2 - 10^6 PFU) induced 100% morbidity and 100% infectivity as determined by weight loss and by TBEV-specific antibody positivity, respectively (Hayasaka et al., unpublished data). Furthermore, all brains infected with low challenge doses contained infectious virus at 9 to 11 days p.i., the period when mice exhibited weight loss (Hayasaka et al., 2009). These observations suggest that CNS pathology is not directly linked to lethality in TBEV infections with late mortality, and whether mice die or survive is determined at late stage of infection, independent of the challenge dose.

3.2.2 Complex mechanism of CNS infection and immune response contribute to late mortality

To examine the mechanism of late mortality in detail, we distinguished dying and recovering/surviving mice by their degree of weight loss following subcutaneous infection with low virus challenge doses of the Oshima strain (Hayasaka et al., 2009). Viral load in the CNS was not as high as intracerebral infection. Interestingly, viral load in the CNS was not significantly different between dying and recovering mice. Histopathological examination showed inflammatory reactions with focal proliferation of microglial rod cells in the brain cortex, thalamus, cerebellum, brainstem and spinal cord in both dying and recovering mice (Hayasaka et al., 2009). These observations suggest that following low challenge dose, mice develop encephalitis but also show features of virus clearance from the CNS. Furthermore, viral infection alone is not a critical determinant of late death, unlike that of early death (Hayasaka et al., 2009).

Inflammatory responses were assessed by measuring cell infiltration and inflammatory cytokine levels in brains (Hayasaka et al., 2009). Infiltrating leukocyte levels including $CD8^+$ T cells, $CD4^+$ T cells, neutrophils, natural killer cell and macrophages were significantly increased in TBEV-infected mice compared with mock-infected mice, but there were no significant differences between dying and recovering mice. Although the levels of inflammatory cytokines involving IFN-γ, IL-2, IL-5 and IL-10 in the brain were increased compared with mock-infected mice, there were no significant differences between dying and surviving mice either (Hayasaka et al., 2009). On the other hand, TNF-α levels were higher in dying mice than in recovering mice, suggesting that TNF-α response in the CNS correlates with severity.

Thymocytes and splenocytes were dramatically decreased in dying mice compared with mock-infected and surviving mice. In addition, corticosterone was most significantly increased in dying mice. These observations suggest that dying mice exhibited a severe stress response.

Serum levels of IFN-γ, RANTES and TNF-α were increased in both dying and recovering mice compared with mock-infected mice (Hayasaka et al., 2009). Interestingly, only serum TNF-α had significantly elevated levels in dying mice compared with surviving mice. Furthermore, among various cytokines examined, IL-10 expression was significantly increased in the spleen of dying mice compared with surviving and mock-infected mice (Hayasaka et al., unpublished data).

These results suggest that fatality is determined by a complex mechanism of CNS pathology and systemic response that involve stress response and increased levels of TNF-α and IL-10.

4. Conclusions

The laboratory mouse model is commonly employed to study the CNS pathology of TBEV *in vivo* because mice develop neurological symptoms and relatively comparable neurological dysfunction similar to that observed in humans (Chiba et al., 1999a; Pogodina and Savinov, 1964; Sokol, Libikova, and Zemla, 1959; Vince and Grcevic, 1969). However, in the mouse model of encephalitic flavivirus infection, dose-independent mortality has been an unresolved problem since the 1940's (King et al., 2007; Lennette, 1944). To explain its mechanism, we recently reported two distinct features of early and late mortality. Late death following low virus challenge doses appears to be a key feature of dose-independent mortality. Furthermore, we have shown that lethal levels of CNS infection cause early mortality, whereas immune and stress responses in addition to CNS infection contribute to late mortality (Hayasaka et al., 2009; Hayasaka et al., 2010). Importantly, whether mice show early or late mortality is associated with the infectious route, virus strain and inoculation dose (Fig. 3).

It is generally believed that human cases succumb to acute and critical neuronal dysfunction following direct viral infection of the neurons, suggesting that early death, as shown in this mouse study, possibly relates to the mechanism of mortality in human cases. Thus, TBEV strains that induce early mortality following peripheral inoculation in mice can be considered as highly virulent and can cause severe disease in humans. Since far-eastern subtypes of TBEV cause more severe disease with up to 20-40% fatality rate in humans, they can be predicted to exhibit early mortality. Contradictory to this however, Oshima, KH and VL strains of Far-eastern subtype exhibit late mortality: infected mice had mild CNS infection and some of them recovered. On the other hand, Sofjin (Far-eastern subtype), Hochosterwitz (European-subtype) and IR strain (Siberian subtype) strains induce early

mortality following peripheral infection, indicating that these strains are potentially more virulent than Oshima, KH and VL strains. Thus, virulence is inconsistent with the TBEV subtype; rather, highly virulent types are more likely to be randomly distributed in endemic areas. In fact, recent studies suggest that seroprevalence rates differ in Europe (1–20%) and in Russia (30–100%), and thus the morbidity and mortality rates may be due to selective severe cases (Lindquist and Vapalahti, 2008).

Our results showed that in addition to CNS infection, systemic stress and inflammatory responses in late phases potentially contribute to the severity and lethality of TBE in human cases. Further elucidation of this mechanism using the mouse model is an important priority to enable the development of effective treatment strategies for human TBE.

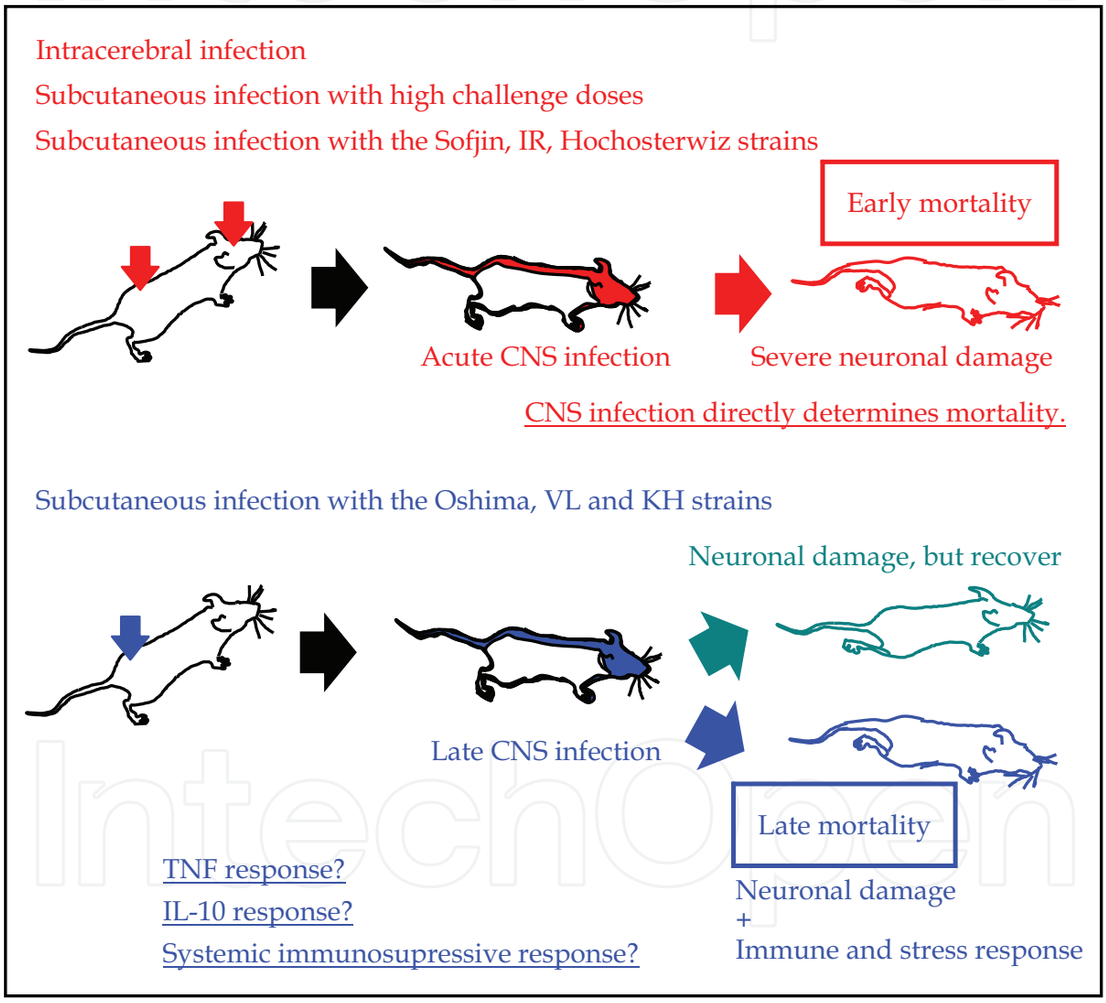

Fig. 3. Summary of early and late mortality observed following TBEV infection in mice

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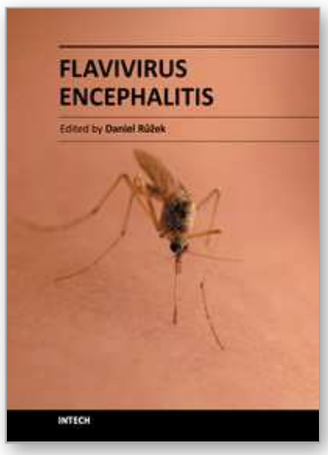

Flavivirus Encephalitis

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

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