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Human Brain Microvascular Endothelial Cells Are Infected By the Tick-Borne Encephalitis Virus, But the Blood-Brain Barrier Is Not Compromised

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Abstract

Tick-borne encephalitis virus (TBEV) is a significant cause of viral encephalitis in humans transmitted by ticks. The central nervous system (CNS) invasion by TBEV poses a serious threat to human health. Understanding the mechanisms underlying the interaction between TBEV and the blood-brain barrier (BBB) is crucial for developing effective therapeutic strategies. Here, we investigated the infection of human brain microvascular endothelial cells (HBMECs) by TBEV and assessed the integrity of the BBB upon viral exposure. Our results demonstrate that TBEV can infect HBMECs without compromising the BBB integrity, suggesting potential avenues for therapeutic intervention in TBEV-induced encephalitis.

Keywords: Tick-borne encephalitis virus, blood-brain barrier, human brain microvascular endothelial cells, viral encephalitis, CNS invasion.

Introduction

Tick-borne encephalitis virus (TBEV) is a member of the Flavivirus genus within the Flaviviridae family, responsible for causing tick-borne encephalitis (TBE), a severe neurological disease in humans. TBEV is primarily transmitted to humans through the bite of infected ticks, particularly Ixodes spp., which are prevalent in forested areas of Europe and Asia [1]. The clinical manifestations of TBE range from mild febrile illness to severe neurological complications, including meningitis, meningoencephalitis, and even death in some cases. Despite the availability of vaccines in endemic regions, TBE remains a significant public health concern due to its potential for causing outbreaks and its lack of specific antiviral treatment [2].

The blood-brain barrier (BBB) serves as a crucial interface between the peripheral circulation and the central nervous system (CNS), regulating the passage of molecules and cells into the brain while protecting it from pathogens and toxins. Understanding the interaction between TBEV and the BBB is essential for elucidating the mechanisms of viral neuroinvasion and developing targeted therapeutic approaches [3]. Previous studies have shown that several neurotropic viruses, including West Nile virus and Japanese encephalitis virus, can breach the BBB by infecting brain microvascular endothelial cells, leading to CNS invasion and neuroinflammation. However, the role of the BBB in TBEV infection and its potential compromise remain poorly understood.

In this study, we aimed to investigate the infection of human brain microvascular endothelial cells (HBMECs) by TBEV and assess the integrity of the BBB upon viral exposure [4]. By elucidating the interplay between TBEV and the BBB, we seek to identify potential targets for therapeutic intervention in TBEV-induced encephalitis.

Materials and Methods

Cell Culture

Human brain microvascular endothelial cells (HBMECs) were cultured in endothelial cell growth medium supplemented with growth factors and antibiotics. The cells were maintained at 37°C in a humidified atmosphere containing 5% CO_2.

Virus Infection

Tick-borne encephalitis virus (TBEV) strain (insert strain details) was propagated in Vero cells and harvested from the culture supernatant. HBMECs were infected with TBEV at a multiplicity of infection (MOI) of 1 for 1 hour at 37°C. After infection, the cells were washed with phosphate-buffered saline (PBS) to remove unbound virus particles.

Immunofluorescence Staining

HBMECs were fixed with 4% paraformaldehyde, permeabilized with 0.1% Triton X-100, and blocked with 5% bovine serum albumin (BSA). The cells were incubated with primary antibodies against TBEV antigens and endothelial cell markers overnight at 4°C, followed by incubation with fluorophore-conjugated secondary antibodies. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI). Fluorescence images were acquired using a confocal microscope.

Transendothelial Electrical Resistance (TEER) Measurement

The integrity of the blood-brain barrier (BBB) was assessed by measuring transendothelial electrical resistance (TEER) using an electrical cell-substrate impedance sensing (ECIS) system. HBMECs were seeded onto gold microelectrodes and allowed to form monolayers. TEER values were recorded before and after TBEV infection to monitor changes in barrier function.

Permeability Assay

The permeability of the BBB to fluorescently labeled dextrans was evaluated to assess barrier integrity. HBMECs were grown on Transwell inserts with 0.4 μm pore size membranes. After TBEV infection, fluorescent dextrans of various molecular weights were added to the

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upper chamber, and their translocation to the lower chamber was measured over time [5,6].

Results

TBEV Infection of HBMECs

Immunofluorescence staining revealed the presence of TBEV antigens in HBMECs following infection, indicating viral replication within endothelial cells. Co-staining with endothelial cell markers confirmed the infection of HBMECs by TBEV.

Integrity of the BBB

Measurement of transendothelial electrical resistance (TEER) showed no significant changes in barrier function following TBEV infection, indicating that the integrity of the blood-brain barrier (BBB) was maintained. Similarly, permeability assays demonstrated no increase in the passage of fluorescent dextrans across the BBB upon viral exposure, further supporting the preservation of barrier function.

Discussion

Our findings demonstrate that human brain micro vascular endothelial cells (HBMECs) are susceptible to infection by tick-borne encephalitis virus (TBEV) without compromising the integrity of the blood-brain barrier (BBB). Despite the ability of TBEV to infect HBMECs, the barrier functions of the BBB remains intact, suggesting that alternative mechanisms may facilitate CNS invasion by the virus. These findings have important implications for understanding the pathogenesis of TBEV-induced encephalitis and identifying potential targets for therapeutic intervention.

Previous studies have suggested that TBEV may exploit other routes, such as transcytosis or immune cell-mediated transport, to cross the BBB and gain entry into the CNS. Further investigation into these mechanisms is warranted to elucidate the dynamics of TBEV neuroinvasion and develop strategies to prevent or mitigate CNS complications. Additionally, future studies should explore the role of host factors and immune responses in modulating BBB permeability during TBEV infection.

In conclusion, our study provides insights into the interaction between TBEV and the blood-brain barrier (BBB) and highlights the importance of preserving BBB integrity in combating viral neuroinvasion. By delineating the mechanisms of TBEV-induced encephalitis, we can pave the way for the development of novel therapeutic approaches to mitigate the neurological sequelae associated with this devastating disease [7-10].

Conclusion

In summary, our findings demonstrate that human brain micro vascular endothelial cells (HBMECs) are susceptible to infection by tick-borne encephalitis virus (TBEV) without compromising the integrity of the blood-brain barrier (BBB). The study concludes that Human Brain Microvascular Endothelial Cells can indeed be infected by the Tick-Borne Encephalitis Virus. However, despite this infection, the integrity of the Blood-Brain Barrier remains intact and uncompromised. This suggests that while the virus can infiltrate specific cells within the brain's vascular system, it does not necessarily lead to a breach in the protective barrier that separates the central nervous system from the bloodstream. Understanding this distinction is crucial for developing targeted treatments and interventions that can combat the virus without compromising the brain's protective mechanisms.

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None

Conflict of Interest

None

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