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Neuroinfections of the Central Nervous System (CNS): Viruses can lead to Serious Neurological Symptoms that may Prove Fatal

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Introduction

Various pathogens can cause neuroinfections of the central nervous system (CNS), but viruses are the most common and can result in severe neurological symptoms with fatal outcomes. Viral infections of the CNS not only directly affect host cells and cause immediate changes in many cellular processes but also trigger a strong immune response. The regulation of this immune response in the CNS depends on microglia, a type of immune cell, and astrocytes, which support blood vessels and ventricle cavities. Astrocytes are among the first cells to become infected by viruses that enter the CNS and are increasingly recognized as a potential reservoir for viruses in the CNS. The immune response to intracellular virus particles within astrocytes can have significant effects on cellular and tissue physiology and morphology, contributing to recurring neurological issues. Various viruses from different families have been confirmed to infect astrocytes. Astrocytes express multiple receptors that detect viral particles and trigger signaling pathways, leading to an innate immune response. This review summarizes current knowledge on virus receptors that activate astrocytes' release of inflammatory cytokines and the role of astrocytes in the immune functions of the CNS [1].

Astrocytes, a type of glial cell, play crucial roles in maintaining the normal functioning of the central nervous system (CNS). They help regulate and support neurons under normal physiological conditions, as well as participate in the development and progression of several CNS diseases. Recent studies on viral infections of astrocytes, along with a better understanding of how viruses modify cellular functions, have increased our knowledge of these cells' functions. Although many viruses cause short-lived infections, some are capable of establishing persistent infections by developing complex relationships with their hosts/host cells and utilizing a wide range of cellular mechanisms for their own benefit. During persistent infection, the virus remains in the host after the primary infection, leading to various types of infections, including chronic focal infection, chronic diffuse infection, latent infection, and abortive infection. These infections differ in the number of infected cells and the effect of the infection on cell viability [2,3]. In contrast to chronic focal and diffuse infections, latent infections can cause recurrent disease episodes triggered by various stimuli but cannot be detected between episodes. Abortive infection does not produce any progeny virus. Various mechanisms, such as non-productive infection, proviral integration, and continuous viral replication, can contribute to persistent infections, and different viruses have evolved unique mechanisms for permanent infections. Nonetheless, they all have the potential to trigger persistent infections by selecting cell subsets ideal for viral genome maintenance, modulating viral gene expression, manipulating cellular apoptotic pathways, and evading the immune system [4]. Astrocytes have multiple roles during inflammation of the CNS, which are influenced by their own intrinsic neurotoxic activities, activation of resident microglia, and recruitment of peripheral inflammatory cells. Astrocytes are activated after insults like brain injury, ischemia, and neuroinfections, including viral infections. Viruses can reach the CNS through various routes and astrocytes are one of the first cells to acquire and replicate them. Astrocytes respond to virus entry by releasing immunomodulatory molecules and participate in the innate immune response. Astrocytes can have a neuroprotective role by producing antiviral mediators that prevent virus replication and dissemination. However, astrocytes can also act as a virus reservoir, promoting virus replication and dissemination in the CNS, and contributing to the long-term presence of the virus in the tissue.

Astrocytes are now known to be important mediators of innate and adaptive immune responses in the damaged Brain. However, the precise processes by which these cells participate in the immune response after viral infection are still being studied. In general, pattern recognition receptors (PRRs) facilitate initial sensing of viral infection by triggering innate immune signalling by recognising viral particles [5,6]. PRRs are proteins that bind to common patterns seen in a variety of pathogens, triggering signalling cascades that activate innate and adaptive immunity. In addition to their role in immune response, astrocytes also contribute to the glymphatic system, a waste clearance system that eliminates soluble proteins and metabolites from the CNS and distributes nutrients and neuromodulators in the brain. Proper functioning of the glymphatic system relies on the presence of aquaporin-4 (AQP4) water channels in astrocyte endfeet, which surround cerebral endothelial cells in the BBB. However, viral infections of astrocytes, such as HIV-1 and EV71, have been associated with decreased expression and mislocalization of AQP4, resulting in the accumulation of extracellular waste products and impaired interstitial flow. In addition, DENV infection has been linked to the development of neuromyelitis optica spectrum disorder, which is associated with AQP4 antibodies affecting AQP4 localization and function in astrocytes. While DENV infection of astrocytes has not been confirmed, this suggests that astrocytes may contribute to the neurologic symptoms of this disorder. Astrocytes play a dual role in viral infections in the CNS. On one hand, their IFN-α/β signaling limits viral spread, but on the other hand, they release cytokines that can disrupt the proper functioning of the CNS [7-10]. One harmful effect is increased permeability of the BBB, which can be triggered by inflammatory cytokines released from astrocytes or by downregulation of tight junction (TJ) genes and upregulation of metalloproteinases that degrade TJ proteins, as seen in various CNS diseases and viral infections such as WNV, TBEV, RABV, and HIV-1 [11]. Dysregulated activation of caspase-1 and IL-1β secretion, as well as NF-κB activation,

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can also contribute to CNS neuroinflammation. In addition, ZIKV infection of astrocytes has been linked to mitochondrial defects, DNA breakage, and glial reactivity, all of which have been associated with neurologic disorders.

Conclusion

To present, only a few studies have looked at morphologic and functional changes in astrocytes as neurodegenerative disorders advance and their consequences on the neurovascular unit in the CNS, and none of them have looked at viral infections. As new neurotropic viruses emerge in the human population and previously believed non-neurotropic viruses are increasingly being linked with neurologic symptoms, the role of astrocytes in the innate immune response to viral infection is receiving interest. In addition to the immediate effects of astrocytes releasing immunomodulatory molecules in the early stages of infection, the implications in chronic inflammation of Brain tissue during long-term infections warrant additional investigation. In addition, it is important to re-evaluate the previously observed alterations in astrocytes regarding viral receptor expression, PPRs, cytokines, and their interaction with neighboring cells. These changes should be assessed based on their potential to cause direct harm to neurons versus their capacity to modulate immune responses, and linked to the resulting dysfunctions in CNS activity.

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Conflict of Interest

Author declares no conflict of interest.

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