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A Brief Review on Neuroinfections of Central Nervous System (CNS) - Triggered by Various Pathogens

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Abstract

Several microorganisms can cause neuroinfections of the central nervous system (CNS). The most common cause of long-lasting neurologic symptoms with potentially fatal consequences is viruses. Viral infections of the CNS not only cause rapid alterations in a variety of cellular processes and have direct effects on their host cells, but they also result in a strong immune response. Microglia, the primary immune cells of the CNS, is essential for the regulation of the innate immune response, although astrocytes also play a role. These cells line along blood arteries and ventricular canals, making them one of the first cell types to contract an infection when the virus enters the central nervous system. A significant impact on cellular and tissue physiology and morphology may result from the immune response triggered by the presence of intracellular virus particles. Moreover, astrocytes are increasingly understood to be a possible viral reservoir in the central nervous system (CNS). Given that they might be a factor in recurrent neurologic sequelae, these alterations should be addressed in terms of lingering infections. A number of viruses, including those from the families Flaviviridae, Coronaviridae, Retroviridae, Togaviridae, Paramyxoviridae, Picomaviridae, Rhabdoviridae, and Herpesviridae, have been demonstrated to infect astrocytes thus far. Many receptors are expressed by astrocytes, which can detect virus particles and start signaling processes that result in an innate immune response. In this review, we describe the current understanding of viral receptors that trigger astrocyte production of inflammatory cytokines and show how astrocytes are involved in CNS immunological processes.

Keywords: Central nervous system; Astrocyte; Glial cells; Neuroinfection; Virus; Immune response; Cytokine; Autophagy

Introduction

Glial cells called astrocytes play important functions in keeping the central nervous system (CNS) in a state of homeostasis [1-3]. In addition to their well-known functions in maintaining and regulating neurons' functionality under normal physiologic circumstances, they also play a factor in the onset and development of a number of CNS disorders [2-5]. A new understanding of how astrocytes contribute to CNS diseases has emerged as a result of growing information on viral infections of astrocytes and growing understanding of how virus infections alter cellular processes (such as upregulation of cytokines, vesicular traffic, and autophagy [6-11]. Viruses from a variety of families, including enveloped positive-sense single-stranded RNA viruses (such as Flaviviridae, Coronaviridae, Retroviridae, and Togaviridae), enveloped negative-sense single-stranded RNA viruses (such as Paramyxoviridae, Rhabdoviridae, and Bunyaviridae), non-enveloped viruses with a single-stranded (Herpeseviridae). Compared to other types of brain cells and endothelial cells that make up the blood-brain barrier (BBB), astrocytes have been shown to play a crucial role in the replication of a number of viruses, including the tick-borne encephalitis virus (TBEV), Japanese encephalitis virus (JEV), Zika virus (ZIKV), West Nile virus (WNV), and Kyasanur virus.

The coronaviruses human coronavirus OC43 (HCoV-OC43), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 may all infect astrocytes (SARS-CoV-2). However not usually, coronavirus infection in astrocytes does not result in infectious virion. La Crosse virus and mosquito-only flavivirus mosquito-borne viruses can also infect astrocytes, however such infections are often non-productive [12]. Induction of a reactive astrogliosis is a frequent feature of neurotropic virus infection. Reactive astrogliosis is the process by which astrocytes engage in molecularly defined programmes in response to pathology that involve changes in transcriptional regulation, as well as biochemical, morphological, metabolic, and physiological remodelling, which ultimately lead to the gain of new function(s) or the loss or upregulation of homeostatic ones. These alterations, together with the activation of the innate immune system, result in the development of neurologic symptoms such as encephalitis, myelitis, postencephalitic parkinsonism, paralysis, and convulsions [13,14]. In this review, we discuss the receptors that astrocytes use to detect viral infection as well as the cytokines that, when produced from astrocytes, have the potential to cause neurologic diseases that frequently resemble specific neurologic illnesses.

Viral infections

Certain viruses are able to create chronic infections despite the fact that the majority of them only cause acute, self-limiting infections. They do this by developing complex relationships with their hosts and host cells and by hijacking a variety of cellular processes for their own purposes. After the first infection, the virus does not leave the host during chronic infection [15]. Chronic focal infections (CFI), chronic diffuse infections (CDI), latent infections, and abortive infections are examples of persistent infections. The number of infected cells and how the infection affects cell viability vary between these infections. In a CDI, all of the cells are infected, and the virus continues to replicate without impacting cell viability. In a CFI, the virus is kept in a limited number of susceptible cells, which release the virus before they die. In contrast

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to CFI and CDI, latent infection causes recurring illness episodes; nevertheless, the virus is undetectable in between these episodes. It's interesting to note that a variety of triggers, including trauma, physical stress, or superinfection by another virus, might revive the infection. Cells do not create any offspring virus during an abortive infection, in contrast to these normal chronic infections.

Many processes, such as nonproductive infection (such as herpesvirus latency), proviral integration into the host genome (such as retroviruses), and/or ongoing viral replication (such as flaviviruses, arenaviruses, and polyomaviruses), can allow persistent infections to persist [16]. Despite the fact that different viruses have developed unique mechanisms to enable long-lasting infections, they all have certain characteristics that have a high likelihood of causing persistent infections. These characteristics include I the choice of cell subsets that are best for long-term maintenance of the viral genome, (ii) modulation of viral gene expression, (iii) viral subversion of cellular apoptotic pathways, and (iv) avoiding immune system clearance. The activation of CNS-resident microglia, the infiltration of peripheral inflammatory cells, and astrocytes' own intrinsic neurotoxic activities all play a part in the many functions that they play during CNS inflammation. Generally speaking, astrocytes begin activating immunological pathways in response to a variety of insults, including brain damage, ischemia, and different neuroinfections, including viral infections [17]. The meningeal blood-cerebrospinal fluid barrier, infected peripheral and olfactory neurons, and endothelial cells of brain capillaries are only a few of the ways viruses can enter the central nervous system (CNS). One of the earliest cell types to pick up and effectively reproduce CNS-invading viruses are astrocytes [18]. These cells quickly release immunomodulatory chemicals in response to viral entrance, contributing to the innate immune response, the initial line of defence against virus infection. It is becoming more widely recognized that astrocytes have a role in both the neurotoxic and neuroprotective effects of the innate immune response in the central nervous system. In the early stages of viral infection, astrocytes' antiviral defences function in opposition, favouring either the host or the virus. The creation of antiviral mediators, which stop virus replication and spread, has a protective function for the host. On the other hand, astrocytes may encourage viral multiplication and spread across CNS cells and function as a virus reservoir to keep the virus present in the tissue for an extended period of time [19].

Viral infections that persist in the central nervous system (CNS) are underappreciated and understudied. Recent studies have suggested that certain CNS viruses, such as TBEV, ZIKV, HIV-1, JEV, CCHFV, and RABV, have the ability to sustain persistent infections of astrocytes. ZIKV-infected activated astrocytes, for instance, have the capacity to multiply inside foci in the mouse brain for more than a year, acting as a ZIKV reservoir. Moreover, for at least a month, human foetal astrocytes may support chronic ZIKV infection and ongoing viral shedding [15]. There in case of ZIKV, supposition has grown that ongoing ZIKV replication and the resulting CNS inflammation with ongoing apoptosis contribute to neurologic deficits and even worsen the long-term neurologic prognosis. However, the relative contribution of ongoing inflammation in the CNS parenchyma, acting to limit the spread of the virus, is still being assessed. A chronic astrocyte infection by EBV has also been hypothesised, but this has to be further investigated along with any possible CNS effects. Astrocytes are clearly involved in both acute and chronic infections of various sorts, according to the ongoing study on their immunological roles. Nonetheless, more research has to be done on the part of astrocytes in certain viral infections. The prolonged infection of astrocytes is particularly noteworthy because it may eventually have an impact on how the Brain functions. The process of infection itself and the regulation of downstream adaptive immunity pathways may be significantly influenced by astrocyte infection that fails and the development of indigenous immune responses. Abortive infection is commonly seen in the experimental setup, and for instance, when the herpes simplex virus (HSV-1) infected the U2OS sarcoma cell line and the cervical cancer cell line HeLa, the viral genome remained in a dormant condition until at least five weeks. Additionally, studies on human astrocytes infected with HIV-1, rat astrocytes infected with TBEV, and the presence of CCHFV and ZIKV in astrocytes of infected mouse brains for several weeks and up to 22 weeks, respectively, provide evidence that astrocytes can establish persistent chronic infection. Due to viral tropism in certain brain areas, prolonged inflammation in the CNS infected with a virus can lead to tissue damage, and immunological responses sparked by viral infection or persistent viral RNA can cause neurologic symptoms to linger long after the virus has been cleared. In the damaged Brain, astrocytes are now understood to be essential mediators of innate and adaptive immune responses. Research is currently being done to determine the precise processes by which these cells contribute to the immune response following viral infection. In general, pattern recognition receptors (PRRs), which start innate immune signaling by recognizing viral particles, facilitate initial detection of viral infection. Innate and adaptive immunity are activated by PRRs, proteins that bind to conserved patterns seen in a variety of pathogens. Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), OAS-like receptors, and AIM-like receptors are only a few of the many receptors that make up the PRR family. The last two in astrocytes have not been mentioned. However, astrocytes modulate the innate immune response in a manner that is comparable to that of CNS-based professional immune cells (microglia, monocytes, macrophages, and dendritic cells) as well as to other nonprofessional immune cells like epithelial, endothelial, and fibroblast cells. In astrocytes, there are both intracellular and cell-surface PRRs that detect viral particles.

TLRs are classic type I transmembrane PRRs that can detect a wide range of foreign pathogens, including bacteria, fungi, viruses, and protozoa. As the virus enters host cells, such as astrocytes, these proteins are among the first receptors to come into contact with viral components and are often activated. TLR-mediated early immune responses inhibit the virus's ability to replicate and propagate. As the internalised viral genetic material from the capsid is released, several types of TLRs enable the detection of viruses from the extracellular space and in the cytoplasm of the host cell in cells that are implicated in the innate immune response. TLRs 3, 7, 8, and 9 are intracellular and presumably signal from acidic endosomes, while TLRs 1, 2, 4, 5, and 6 are located in the plasma membrane in cells generally. TLRs in endosomes or endolysosomes detect virus genetic material. These TLRs include TLR3, which senses double-stranded intermediate RNA (dsRNA), TLR7 and TLR8, which sense single-stranded RNA (ssRNA), and TLR9, which senses double-stranded DNA (dsDNA). All plasma membrane TLRs recognise virus glycoproteins of enveloped viruses.

A particular class of intracellular proteins known as NLRs is essential for controlling the host's innate immune response. The pathophysiology of several inflammatory illnesses is linked to excessive NLRP3 activation; for a summary. These cytosolic receptors function as scaffolding proteins that facilitate the construction of signalling platforms, which in turn activate signalling pathways including NF-B and mitogen-activated protein kinase (MAPKs) and regulate the activation of inflammatory caspases. According to their N-terminal

effector-binding domain, the 23 NLRs that have been described in humans have been divided into five subfamilies: acidic transactivation domain (NLRA); baculovirus inhibitor repeat, BIR (NLRB); caspase recruitment domain, CARD (NLRC); pyrin domain (NLRP); and NLRX1. While they are also expressed in epithelial cells and astrocytes, macrophages and neutrophils are the primary phagocytes where NLRs are found.

It's possible that astrocyte viral infection has a significant impact on how well the glymphatic system works. Glucose, lipids, amino acids, growth factors, and neuromodulators are distributed more easily in the brain thanks to the glymphatic system's perivascular tunnels, which are shaped by astrocytes and serve as a waste clearance system for the removal of soluble proteins and metabolites from the CNS. Astrocytic endfeet that surround cerebral endothelial cells in the BBB assist the proper operation of the glymphatic system. Condensed localization of aquaporin-4 (AQP4) water channels, which facilitate the interchange of interstitial and cerebrospinal fluid, is one of the characteristics of astrocyte endfeet. It's interesting to note that HIV-1 infection causes AQP4 to express less and to mislocalize, which reduces interstitial flow and causes extracellular waste products to accumulate. Several neurotropic viruses can infect the Brain and cause this effect. For instance, an EV71 infection of a mouse brain has shown that AQP4 is mislocalized [21]. Similar to this, DENV infection has been linked to the onset of neuromyelitis optica spectrum illness; AQP4 antibody was detected in the patients' serum [22]. This does not yet have a known pathophysiologic mechanism. While astrocyte infection by DENV has not been shown, AQP4 antibodies that impact AQP4 location and function in astrocytes suggest that this cell type may be involved in the neurologic symptoms of neuromyelitis optica spectrum disease. Virus-infected astrocytes can have conflicting effects on the survival of neurons. One the one hand, it has been shown that the innate immune response in astrocytes is critical for the damage to dopaminergic neurons and the onset of Parkinson disease-like pathology, for instance, in instances of infections with WEEV and WNV. On the other hand, astrocytes can inhibit viral propagation in astrocytes and other CNS cells, including neurons, and increase cell survival by boosting the type I IFN response. According to a recent investigation using MHV-A59-infected astrocyte persistent cell lines, astrocytes of different morphologies responded to infection by producing pro-inflammatory cytokines in varied ways. Future studies on astrocyte infection with viruses that cause neurologic symptoms must take into account the fact that astrocytes may adopt multiple phenotypes in reactive astrogliosis, a frequent result of astrocyte infection, which should be defined by a combination of molecular markers and functional readouts.

Discussion

Several research have examined the morphologic and functional alterations in astrocytes that occur as neurodegenerative disorders advance and their implications on the CNS's neurovascular unit; none of these studies, however, have specifically addressed viral infections. As more neurotropic viruses are discovered in the human population and previously thought non-neurotropic viruses are increasingly linked to neurologic symptoms, the role of astrocytes in the innate immune response to viral infection is receiving more attention.

Conclusion

The implications for chronic inflammation of the CNS tissue during long-term infections also need additional study, in addition to the immediate effects of the release of immunomodulatory chemicals from astrocytes in the early stages following infection. The changes in astrocytes' expression of viral receptors, PPRs, and cytokines as well as their interactions with neighbouring cells need to be revisited in order to determine whether they have direct neurotoxic effects or indirect immunomodulatory effects, and to determine whether they are associated with difficulties of Central nervous system functions.

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Conflict of Interest

Author declares no conflict of interest.

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