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Review Article

Pathogenesis of enterovirus infection in central nervous system

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ABSTRACT

Enteroviruses (EVs) are classified into 15 species according to their sequence diversity. They include four human EV (A, B, C, and D) and three rhinoviruses (A, B, and C), and cause diseases in millions of people worldwide. Generally, individuals with enteroviral infections have mild clinical symptoms, including respiratory illness, vomiting, diarrhea, dizziness, and fever. More importantly, some members of the human EV family are neurotropic pathogens that may cause a wide range of clinical diseases, such as aseptic meningitis and encephalitis. Previously, the EV that caused the most severe neurotropic symptoms was poliovirus (PV), a member of the EV C group. Poliovirus has been eliminated in most countries through a global vaccination campaign. Non-PV EVs infect the central nervous system (CNS) and are the major EVs causing neurological diseases. These human non-PV EVs include EV A (e.g., EV-A71, CVA6, and CVA16), B (e.g., CVA9 and CVB3, CVB5, echovirus 11 [E11], E30, and E7), C (e.g., CVA24), and D (e.g., EV-D68). Here, we review the relationship between EV infection and CNS diseases and advance in the use of cellular receptors and host immune responses during viral infection.

1. Introduction

Enteroviruses (EVs) are the most common viruses that infect humans [1]. Currently, 116 serotypes have been reported, many of which are highly prevalent worldwide. EV belongs to the genus Enterovirus, family *Picornaviridae*, with multiple serotypes. EV virions are icosahedral, with a diameter of approximately 30 nm. The virus particles lack a lipid envelope and are simple, consisting of a protein shell surrounding the naked RNA genome [2]. The EV genome is single-stranded RNA with a length of approximately 7.4 kilobases. Three sub-regions, P1, P2, and P3, constitute the coding region of EV. The P1 region encodes the viral structural proteins VP1, VP2, VP3, and VP4 [2]. EVs include coxsackievirus groups A (CVA) and B (CVB), echoviruses (E), and polioviruses (PV). With the emergence of an increasing number of unknown EVs, human EVs are classified into four types by molecular typing: EVA, EVB, EVC, and EVD [3]. EVs are mainly transmitted through the fecal-oral route, and while they usually cause mild subclinical disease, they can also cause severe disease [4]. For example, EVs are the most common cause of aseptic meningitis, which is usually milder than bacterial meningitis, but is more frequent [5]. Tens of thousands of people are hospitalized for aseptic meningitis each year in the United States alone, resulting in an enormous economic and social burden [6]. Various viruses can cause aseptic meningitis, including herpes virus, influenza virus, mumps virus, and arbovirus [7–9]. However, since the widespread use of the mumps, measles, and rubella vaccine, EVs have become the main pathogen causing aseptic meningitis.

2. EVs and central nervous system (CNS) diseases

The blood–brain barrier (BBB) protects the central nervous system (CNS) from most pathogens, and homeostasis is maintained by neurons, microglia, and astrocytes [10]. However, EVs have evolved the ability to invade the nervous system and infect the CNS [11,12]. EVs can cause severe diseases, such as aseptic meningitis, encephalitis, acute flaccid paralysis, and acute flaccid myelitis [13–16]. Paralytic diseases, such as acute flaccid myelitis, have been most commonly linked to EV-D68 and EV-A71 infections, but these illnesses have also been associated with several of the more recently identified rare non-polio EVs, such as EV-C105 and EV-C109 [17]. EV-A71, CVA6, and EV-D68 can cause severe infections, and E30, E15, E6, CVB3, and others

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have been shown to cause CNS infections [5,11,12,18,19]. These viruses enter the human body, cause an early local inflammatory response, and induce tissue-specific antiviral responses in the surrounding cells [20]. The viruses can spread to other tissues from the primary site of infection, with serious consequences for the CNS [21]. The causative agents of both the EV-D68 and EV-A71 outbreaks were eventually identified by the striking severity of the disease and their rapid emergence, but this identification was considerably delayed by the low rate of diagnostic detection and timely virus type identification. Surveillance relies on rapid case detection, reporting, and epidemiological and laboratory investigations. For example, in 2017, an Asia Pacific enterovirus surveillance network (APNES) was established to estimate the disease burden, understand virus evolution, and promote vaccine development by coordinating laboratory diagnosis and data collection [22], and the European Non-Polio Enterovirus Network (ENPEN) was recently established to develop and share diagnostic technical knowledge on EV detection and characteristics, disease manifestations and prognosis, virus evolution, and pathogenesis [23]. Although some EV surveillance networks have been established worldwide, most of them are based on case surveillance systems. However, EV infections are systemic infections with the digestive tract as the primary focus. Therefore, it is difficult to reflect the true prevalence of EVs without an EV etiology surveillance system.

Table 1
Enterovirus (EV) receptors.

Virus	Receptor	Role	References
EV-A71	SCARB2	uncoating	[25]
EV-A71	PSGL-1	attachment	[32]
CVA16	SCARB2, PSGL-1	uncoating	[25,27]
CVA6	KREMEN1	attachment/uncoating	[34]
CVA10	KREMEN1	attachment/uncoating	[35]
EV-B	FcRn	uncoating	[46]
CVB3	DAF	attachment	[38]
CVB3	CAR	uncoating	[39]
CVA9	αVβ3, αVβ6 integrins	attachment	[49]
E11	FcRn	attachment	[43]
Poliovirus	PVR (CD155)	uncoating	[50]
CVA24	ICAM-1	uncoating	[52]
EV-D68	ICAM-5	uncoating	[55]

The current classification of enteroviral receptors and attachment factors is based on the ability of cell surface molecules to initiate viral uncoating (receptor) or their ability to allow cell surface attachment but insufficient to cause genome release (attachment factors). Abbreviations: EV-A71, enterovirus A71; CVA16, coxsackievirus A16; EV-B, enterovirus B; CVB3, coxsackievirus B3; CVA9, coxsackievirus A9; E11, echovirus 11; EV-D68, enterovirus D68; SCARB2, Scavenger receptor class B member 2; PSGL-1, P-selectin glycoprotein ligand-1; FcRn, human neonatal Fc receptor; DAF, decay-accelerating factor; CAR, coxsackievirus and adenovirus receptor; PVR, poliovirus receptor; ICAM-1, intercellular cell adhesion molecule-1; ICAM-5, intercellular cell adhesion molecule-5.

3. EV receptors

The cell surface receptors used by viruses for attachment and invasion are key factors in viral pathogenesis. Virus receptors refer to host cell membrane components that can specifically bind to viruses, mediate virus invasion, and promote virus infection. Their chemical essence is glycoproteins, proteoglycans, lipids, or glycolipids, most of which belong to proteins. EVs initiate infection of cells by first binding to a receptor on the host cell's plasma membrane. Different types of cell surface molecules serve as cellular receptors for EVs (Table 1). For some EVs, a single type of receptor molecule is sufficient for viral binding and entry. These include the cellular receptors for poliovirus (poliovirus receptor, PVR) and rhinovirus (intercellular cell adhesion molecule-1, ICAM-1). For some EVs, interaction with only one receptor is not sufficient for infection, for example, CVA21 binds to decay-accelerating factor (DAF), but infection does not occur unless ICAM-1 is also bound [24].

Among the neurotropic EV-A, EV-A71 receptors are the most widely studied. Scavenger receptor class B member 2 (SCARB2) is a common receptor for EV-A strains including EV-A71 and CVA16 [25–27]. In the CNS, it mediates the binding of EV-A71 to neuronal cells, allowing the virus to infect neuronal cells and subsequently causing neurological disease [28]. In addition, SCARB2 expression has been detected in brain neurons and skeletal muscles in human biopsies [29,30]. In addition, VP1-145 is a key factor in EV-A71 binding to P-selectin glycoprotein ligand-1 (PSGL-1) [31]. However, there is no evidence that PSGL-1 is involved in neuropathic damage, possibly due to its primary expression in the leukocytes [32]. CVA6 and CVA10 are also common pathogens that often cause neurological symptoms. KREMEN1 is the entry receptor for the largest receptor-group of hand, foot, and mouth disease (HFMD) causing viruses, which includes CVA6 and CVA10 [33,34]. CVA10 uses the two-in-one attachment and uncoating receptor KREMEN1 [35,36].

As the largest subgenus of EVs, EV-B includes more than 60 serotypes [37]. For example, CVB3 can infect the neonatal ventricle and accelerate the damage of neural progenitor cells, which is closely related to two major receptors, the decay-accelerating factor (DAF) [38] and the coxsackievirus and adenovirus receptor (CAR) [39]. Furthermore, recent studies have shown that CAR is highly expressed in immature neurons and prefers the same pH that also promotes CVB3 shedding [40–42]. Echoviruses are the largest group of EV-B, and they can cause severe CNS diseases in neonates [43–45]. The human neonatal Fc receptor (FcRn) is the uncoating receptor for major EV-B [46,47]. Moreover, FcRn can mediate severe E11 infection in suckling mice, but only when they are interferon-deficient, suggesting that interferon signaling may be important for age-related susceptibility [43]. DAF receptors are co-receptors of echoviruses, but without FcRn, the endothelial cells are not susceptible to echovirus infection [43,48]. The αVβ3 and αVβ6 integrins are the attaching receptors of CVA9 [49].

Among the neurotropic EVs, PV receptors are the most extensively studied, and CD155 is considered the only receptor for PV [50]. CVA24, an EV-C member, causes acute hemorrhagic conjunctivitis (AHC) [51] and meningitis [20]. The intercellular adhesion molecule-1 (ICAM-1) can interact with the capsid protein of CVA24, thus, promoting the early stage of AHC, but the neurotropic potential of CVA24 has not been well studied [52].

As a member of EV-D, EV-D68 causes severe respiratory disease and is primarily airborne. It is associated with the neurological symptoms of acute flaccid myelitis [53,54]. Although the pathogenesis of EV-D68 remains unknown, recent *in vitro* studies have shown that EV-D68 interacts with neuron-specific intercellular adhesion molecules, leading to viral shedding and neurotropism [44,55–58].

4. EV invasion of the CNS

EVs use various strategies to invade the CNS. Generally, EVs are transmitted via the fecal-oral route and replicate in the gastrointestinal tract. EV-A71 can infect the CNS by several routes [59]. EV-A71 mainly infects the intestinal mucosal epithelium and lymphoid tissues outside the CNS , but has also been detected in the blood [18,60]. Similar to PV, EV-A71 enters the CNS mainly by retrograde axonal and cross-synaptic transport, and viral shedding occurs inside the CNS cells [61,62]. In addition, the viruses CVB3 and EV-A71 directly penetrate the BBB, which usually restricts the entry of macromolecules and

pathogens into the CNS by infecting B [63] and T lymphocytes [64]. EV-A71 may enter the CNS by infecting macrophages; however, the specific mechanism requires further investigation. Furthermore, neurotropic EVs, such as PV and EV-A71, can directly cross the BBB and infect brain microvascular endothelial cells [2]. E30, which causes meningitis outbreaks, infects the papilloma cells of the brain choroid plexus and invades the CNS via the cerebrospinal fluid barrier (BCSFB) [65].

5. EV cell tropism

Due to the limited number of specimens from patients with EV-related CNS diseases, neuroblastoma, and glioblastoma cells are mostly used in laboratory studies. Each neurotropic enterovirus targets different cell types [66,67]. PV infection results in severe poliomyelitis that mainly affects the anterior horn motor neurons of the spinal cord and brainstem neurons, and PV antigen has been detected in these areas in mice [68–70]. EV-A71 can infect the brain stem and neurons of the anterior horn of the spinal cord, as well as the peripheral nerves of the CNS, including the cranial nerves [71,72], the spinal motor neurons [73,74] and the enteric autonomic nerves [75]. Similarly, the virus can infect the CNS via the peripheral nerves. CVB3 can infect neurons [76] and tends to infect proliferative neural progenitors [77], which may be associated with high CAR expression in immature neurons [78].

Additionally, astrocytes can be infected by CVB [79]. EV-A71 invades the CNS by infecting motor neurons at neuromuscular junctions (NMJs) [80]. In infected mice, peripherin colocalizes with viral antigens in the NMJs and spinal cord but plays no role in CVA16 infection [81]. Interestingly, EV-A71 infected macrophages and $CD15^{+}$ neutrophils and caused severe CNS inflammation. Neutrophils were particularly abundant in tissues other than those in the CNS, suggesting that inflammatory cells play an important role in the entry of EV into the CNS [82,83]. These neurotropic EVs cause acute CNS diseases; however, some cause long-term damage after acute infection [84]. PV has accumulated various mutations that allow the virus to evade the immune system and maintain a persistent infection [85]. One study showed that EV-A71 could persistently infect the brain of immunodeficient mice [86]. Additionally, E30 can significantly increase the resistance of HIBCPP cells, which interferes with the performance of BCSFB. The virus can also infect human glioma cells, but the exact mechanism by which these cells are infected remains unclear [87].

6. Inflammatory response caused by EV infection

Although encephalitis and meningitis occur in only a small percentage of people infected with EVs, the inflammatory response that occurs after the host recognizes the virus usually leads to severe symptoms [88]. In contrast, the immune response of the central nervous system to the transmission of congenital EV may be harmful. In this case, congenital transmission of CVB to the brain can lead to an inflammatory immune response, characterized by increased levels of proinflammatory cytokines, chemokines, and inflammatory cell infiltration, as well as tissue damage. Elevated cytokines associated with infection can be harmful. Thus, fetal CNS infection with CVB may lead to fetal infection with life-threatening diseases or become a source of brain damage [89]. The retinoic acid-inducible gene (RIG)-I-like receptor serves as a cytosolic sensor for viral RNA bases, initiating antiviral and inflammatory cellular responses. The interaction between helicases and viral RNA induces the recruitment of downstream effector molecules, including mitochondrial antiviral sig naling (MAVS), tumor necrosis factor receptor-associated factor (TRAF) 3, and possibly stimulator of interferon gene (STING), leading to the activation of IκB kinase (IKK) -associated kinases, TRAF family members associated NF-κB activator-binding kinase 1 (TBK1), and IKK-I. These kinases activate the transcription factors NF-κB and interferon regulatory factor 3 (IRF3), which translocate to the nucleus and activate the transcription of IFN-stimulated genes and inflammatory factors. In addition, MyD88 mediates the activation of IRF-7 and thus the expression of type I interferon. Understanding the molecular mechanisms of viral replication may help us to develop strategies to control viral infection (Fig. 1). The release of inflammatory cytokines promotes chemokine and leukocyte recruitment, leading to an interferon response [90]. However, these inflammatory cytokines may be more damaging to the CNS than the viral infection itself [91]. CVB3 infection recruits large amounts of the chemokine CCL12 [92], which causes myeloid cells to enter the CNS. In general, immune cells in the peripheral blood do not penetrate the BBB, which may be related to the immune signals monitored by the BCSFB. In the cases of death from encephalitis caused by EV-A71, neurogenic pulmonary edema mainly results from CNS inflammation, and some pro-inflammatory cytokines, such as IL-1, IFN-γ, and IL-10, are highly expressed in patients with pulmonary edemas [60,93,94]. In addition, infection of astrocytoma cells with EV-A71 and CVA9 could induce the production of VCAM-1, IL-6, and IL-8 [95], while IL-6 and IL-8 were upregulated in primary mouse astrocytes and human glioma cells infected with EV-A71 [96]. As these chemokines are effective chemokines, they may help guide neutrophils and monocytes/macrophages to the infection sites within the CNS. Primary mouse astrocytes and human glioma cells infected with EV-A71 induced STAT3 expression, which interfered with STAT1 translocation to the nucleus and inhibited the production of ISGs, thereby inhibiting the antiviral response mediated by type I interferon [96]. During virus-induced CNS inflammation, microglia play a role in regulating immune signaling pathways, which can be activated to produce tumor necrosis factor alpha (TNFα), IL-6, and other inflammatory factors during infection [97,98]. In addition, astrocytes secreting trophic factors are also infected by neurotropic EVs, which increase BBB permeability and increase their susceptibility to viral invasion. Rac1 signaling pathway has been reported to be involved in cancer and neurodegenerative diseases [99,100]. After EV-A71 infects SK-N-SH cells, Rac1 induces active reactive oxygen species signaling by activating NADPH oxidases, thereby enhancing viral replication [81]. EVs have evolved the ability to evade the host's antiviral response. For example, PV disrupts the interferon signaling pathway by reducing RIG-1 levels, whereas EV-A71 blocks the recruitment of IPS-1 by binding RIG-1 to the 3C protease [101]. In addition, EV-D68 has been reported to suppress innate antiviral immunity by down-regulating interferon regulatory factor 7 (IRF7) [102]. This process depends on 3Cpro, an EV-D68-encoded protease, to mediate IRF7 cleavage. When expressed in host cells, 3Cpro targets Q167 and Q189 within the constitutive activation domain, resulting in the cleavage of IRF7 [102]. The latest research [103] shows that EV-D68 infection can induce TDP-43 cleavage and aggregation, leading to neurotoxicity. TDP-43 is a protein that is associated with neurodegenerative diseases. Under normal conditions, TDP-43 mainly exists in the nucleus and is involved in gene transcription and splicing. They also found that Nsp5, the major protease encoded by EV-D68, is a key factor in the cleavage of TDP-43 and can be hydrolyzed at amino acid position 327 of TDP-43. At the same time, a variety of antiviral drugs were screened, and it was found that lopinavir could inhibit the activity of Nsp5, thereby alleviating the TDP-43 abnormalities and neuronal death caused by EV-D68 infection. These results may lead to a better response to neurotropic enteroviral infections in cell culture.

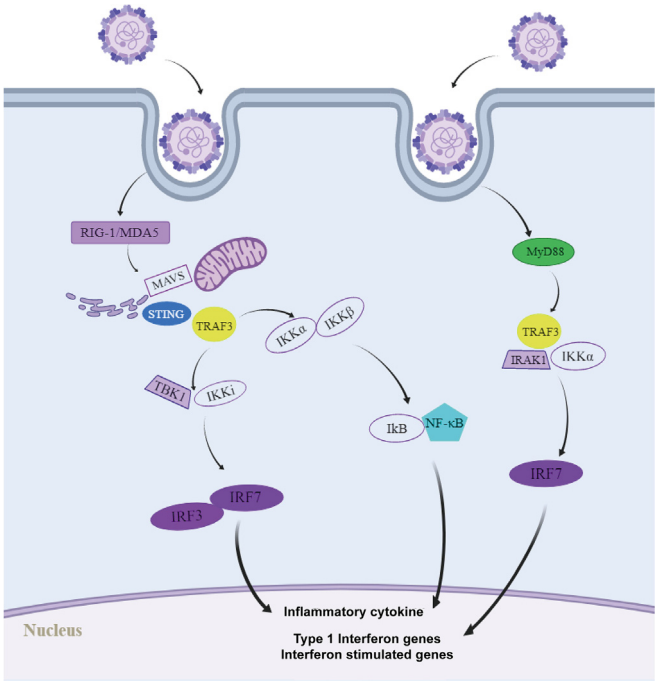

Fig. 1. The molecular mechanisms of the immune response to enterovirus (EV) infection. The retinoic acid-inducible gene (RIG)-I-like receptor serves as a cytosolic sensor for viral RNA bases, initiating antiviral and inflammatory cell responses. MyD88 activates the downstream inflammatory pathways, activating the transcription and expression of many inflammatory factors. The figure was created using MedPeer's online scientific drawing tool. (https://image.medpeer.cn/show/index/index). Abbreviations: MAVS, mitochondrial antiviral signaling; STING, stimulator of interferon gene; TRAF, receptor-associated factor; TBK1, TANK-binding kinase 1; IRAK1, Interleukin-1 receptor-associated kinase 1; IKK, IκB kinase; IRF, interferon regulatory factor.

7. Conclusion

As one of the most common human pathogens among small RNA viruses, EVs can cause systemic dissemination and CNS diseases and pose a heavy societal burden. It is currently unclear whether systemic dissemination directly leads to CNS invasion, or whether systemic transmission occurs even during mild or subclinical diseases. In addition, it is currently unclear whether EVs-associated paralysis is always the result of CNS invasion and infection of motor neurons, or whether EV invasion of muscle tissue directly leads to paralysis. Therefore, it is important to have a deep understanding of the systemic pathogenesis of EVs, including the cell and tissues tropism, as well as the roles of viruses and host factors. This information is critical to understanding disease progression and early detection after disease onset. Much remains to be learned about how EVs invade the CNS and evade host immune responses, as well as their pathogenesis. In summary, the relationship between CNS diseases and EVs has been reviewed to improve our understanding of the neuropathogenesis of EV infection. However, further studies on viral genotypes, virulence genetic factors, and ways to evade the host immune response are needed.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Congcong Wang: Conceptualization, Investigation, Writing – review & editing. **Jichen Li:** Conceptualization, Investigation, Writing – review & editing. **Ying Liu:** Conceptualization, Writing – review & editing. **Qiang Sun:** Conceptualization, Writing – review & editing, Supervision. **Zhijun Liu:** Conceptualization, Supervision.

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