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REVIEW

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An update on enterovirus 71 infection and interferon type I response

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Summary

Enteroviruses are members of Pichornaviridae family consisting of human enterovirus group A, B, C, and D as well as nonhuman enteroviruses. Hand, foot, and mouth disease (HFMD) is a serious disease which is usually seen in the Asia-Pacific region in children. Enterovirus 71 and coxsackievirus A16 are two important viruses responsible for HFMD which are members of group A enterovirus. IFN α and β are two cytokines, which have a major activity in the innate immune system against viral infections. Most of the viruses have some weapons against these cytokines. EV71 has two main proteases called 2A and 3C, which are important for polyprotein processing and virus maturation. Several studies have indicated that they have a significant effect on different cellular pathways such as interferon production and signaling pathway. The aim of this study was to investigate the latest findings about the interaction of 2A and 3C protease of EV71 and IFN production/signaling pathway and their inhibitory effects on this pathway.

KEYWORDS

2A protease, 3C protease introduction, enterovirus 71, interferon type I

1 | INTRODUCTION

Enteroviruses are members of Pichornaviridae family, which include human enterovirus group A, B, C, and D as well as nonhuman enteroviruses.[1] Hand, foot, and mouth disease (HFMD) is a serious disease which is usually seen in Asia-Pacific region in children. Enterovirus 71 and coxsackievirus A16 are two important viruses responsible for HFMD which are members of group A enterovirus.[2,3] After poliovirus eradication, EV71 was recognized as an important norotropic virus. Enterovirus 71 was first detected in 1969 in California and isolated from a child's feces suffering from encephalitis.[4] Enterovirus 71 infection is usually seen as children exanthema, yet it can cause neurologic diseases such as aseptic meningitis, encephalitis, and flaccid paralysis.[5] EV71 is divided to three subgenotypes including group A containing prototype strain BrCr, group B, and group C with each categorized as B1 to B5 and C1 to C5 subgroup responsible for several outbreaks in southeast Asia, Europe, and Australia.[3,5-12] These viruses have a positive sense single-stranded RNA with an approximate length of 7400 nucleotides, consisting of four structural viral proteins 1 to 4 (VP1-VP4) and seven nonstructural proteins (2A-2C and 3A-3D).[13,14] This genome has one large open reading frame (ORF) which translates to a large polyprotein and flanks with an untranslated region (UTR) on the 5′ side (750 nucleotide) and another untranslated region on the 3′ side (75-100 nucleotide).[15] HFMD is mostly a mild and self-limiting disease, but it can progress to create serious neurologic diseases specially in acute infection, which in rare cases can be seen in coxsakievirus A16.[5,16] Yet, there is not any vaccine or drug for HFMD.[17] The infection cycle of enteroviruses consists of different stages: After entering the cell and uncoating, positive sense single-stranded RNA, which has one ORF, acts as an mRNA and translates to one large polyprotein, which will be processed by viral proteases and lead to release of different structural and nonstructural viral proteins. Viral RNA is replicated through synthesis of a complement negative strand in the cytoplasm by viral 3D protein as

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an RNA-dependent RNA polymerase (RDRP). RNA synthesis occurs in the replication complex on the outer surface of membrane vesicles which have been induced by virus.[18] The new synthesis RNA, which is released from the replication complex, may enter another round of translation and replication or package through capsid proteins to produce progeny virus. Initiation of new genome strand polymerization depends on RDRP position. In this regard, for negative strand synthesis, RDRP should be close to 3′ end of the positive strand, and for positive strand synthesis, RDRP should be close to 3′ end of the negative strand. Because of difference in 3′ end in complement strands, the replication machine recognizes two different origins of replication for initiation of positive and negative strand synthesis called OriL and OriR, respectively.[1] Numerous studies have indicated that 5′ and 3′ UTR of enteroviruses have an important effect on tissue tropism and pathogenesis.[19,20] Some studies indicate that VP1 BC loop of EV71 (L97R) has an important role in viral tropism.[21] After EV71 infection, different organs are attacked by the virus causing gastrointestinal, cardiac, pulmonary, and neurologic disease. Recently, hscARB2 and PSGL-1 have been recognized as a receptor for EV71.[22,23] EV71 also uses SA-linked glycans as a receptor for infection.[24]

2 | INTERFERON PATHWAYS, THE FIRST DAM AGAINST VIRAL INFECTIONS

Interferon family is divided into three class of cytokines, including types I, II, and III, among which type I is expressed in nearly all mammalian cells,[25] which consists of α, β, ω, ε, and κ. On the other hand, only one type has been observed in the IFN II family called IFN-γ which has an immunomodulatory effect on the immune system and antiviral activity. This kind of interferon is produced only by activating T cells or NK cells.[25] Type III interferon has three subtypes including λ1, λ2, and λ3 which are induced by viral infection and show antiviral activities.[26] Among these molecules, IFN α and β are two cytokines with a major activity in the innate immune system against viral infection.[27] After a viral infection, IFN response is induced in two stages: IFN production pathway is induced followed by IFN signaling pathway (Figure 1). Viral genomes such as DNA and RNA or intermediate replicative double-stranded RNA (dsRNA) recognized as pathogen-associated molecular patterns (PAMP) are essential for inducing IFN α and β production through pattern recognition receptors (PRR) including toll-like receptors (TLR)[28] and RIG1-like receptors (RLR).[29,30] Single-stranded viral RNA and dsRNA are recognized by TLR7/8 and TLR3 in endosome or by melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene 1 (RIG1) in the cytosol. Endosomal TLRs recognize viral nucleic acids with an outer source which enter the cell through endocytosis, where MDA5 and RIG1 detect viral nucleic acids present in the cytosol.[31] After recognition of dsRNA by TLR in the endosome, toll interlukin-1 receptor (TIR) is recruited, causing activation of another adaptor called TIR domain-containing adapter-inducing interferon-β (TRIF). TRIF with another protein called TNF receptor-associated factor 3 (TRAF3) leads to activation of two IKK-related kinases including TANK-binding kinase 1 (TBK1) and "I kappa B kinase I" (IKKi). These two adaptors mediate phosphorylation of interferon regulatory factor 3/7 (IRF3/7) and induce IFN type I expression.[32-35] Viral ssRNA in endosomes is recognized by TLR7 and TLR8 and recruiting other adaptors such as myeloid differentiation primary response 88 (MYD88) and TRAF6,[36] resulting in the activation of interleukin 1 receptor-associated kinase 1 (IRAK1) kinase followed by phosphorylation of IRF7, where IRF7 transports to the nucleus and induces IFN type I expression.[37] Meanwhile, there are other alternative mechanisms for cytosolic nucleic acids. Two RNA helicase RIG1 and MDA5 recognize viral RNA in the cytoplasm, after which IFN promoter-stimulating factor 1 (IPS1, Cardif, MAVS, or VISA) is recruited. Then, the interaction between IPS1, TRAF3, and TBK1/IKKi leads to activation of IRF3/IRF7 and induction of IFN type I expression.[38] The IFN production pathway has been demonstrated in Figure 1. It is observed that MDA5 recognizes long dsRNA such as the replicative form of picornavirus genome and other virus families including coronavirus and calcivirus. On the other hand, RIG I is sensitive to double-stranded RNA (dsRNA) with 5′ triposphate (5′ppp) and some double-stranded sequences within ssRNA molecules formed by RNAs of negative strand RNA viruses. However, some other reports suggest that RIG1 recognizes 5′ppp single-stranded RNA with poly A/U motif and short dsRNAs.[38-43] After a burst of IFN type I in infected cells, it is released from cells and attached to an interferon receptor on the adjacent cells. After attachment of IFN to interferon receptor 1 (IFNR1) and interferon receptor 2 (IFNR2), two protein kinases including Janus kinase1 (JAK1) and tyrosine kinase 2 (TYK2) are activated via phosphorylation resulting in activation and phosphorylation of signal transducer and activator of transcription 1 (STAT1) as well as signal transducer and activator of transcription 2 (STAT2) proteins. These two proteins create a heterodimer and interact with IRF9 to produce interferon-stimulated gene factor 3 (ISGF3) complex. The phosphorylated STAT1 interacts with karyopherin subunit alpha 1 (KPNA 1) which acts as a nuclear localization signal (NLS) receptor and recognizes STAT1 NLS which facilitates ISGF3 translocation to the nucleus and induces interferon-stimulated gene (ISG) expression.[44]

3 | 2A AND 3C PROTEASES

2A protease is translated firstly during the translation of the nonstructural region (P2) of enterovirus polyprotein. It then separates itself from P2 and P1 regions through self-cleavage. This process then continues with the P3 region, which contains the second protease called 3C, responsible for 8 out of 10 cleavages of the viral polyprotein. Finally, these cleavages lead to production of 11 structural and nonstructural proteins including VP1, VP2, VP3, VP4, 2A, 2B, 2C, 3A, 3B, 3C, and 3D.[45] 2A and 3C are cysteine proteases, belonging to the chymotrypsin-related endopeptidase protease family.[46] The protein sequence alignments of 2A and 3C show only ~20% similarity, but they have similar tertiary structures. Different enterovirus genotypes have shown approximately 50% to 75% sequence similarity in 2A and 3C. The tertiary structures of 2Apro reveals a six-stranded antiparallel β-sheet barrel and a β-sheet pile packed on its side. 3Cpro has a tertiary structure consisting of the twisted ß-barrels packed perpendicular to each other. These domains help to create a catalytic site,

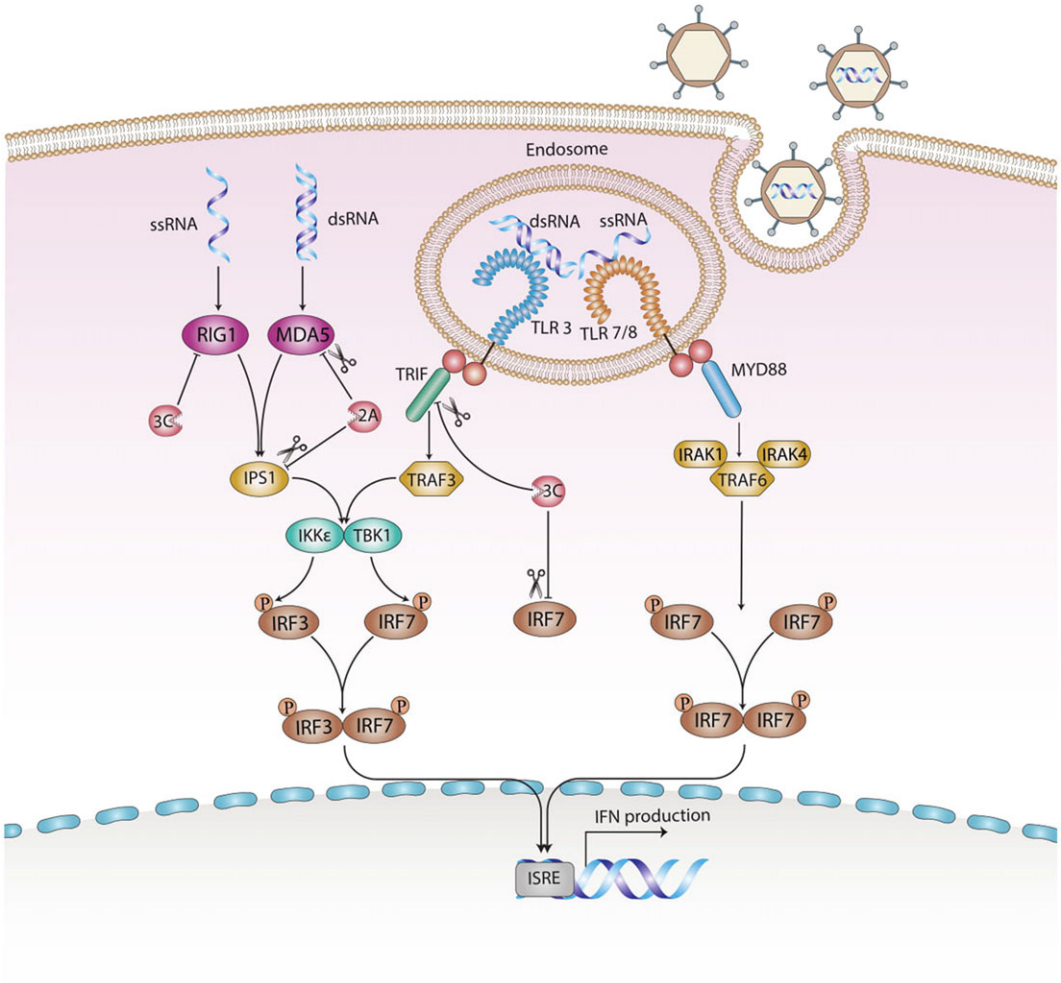

FIGURE 1 IFN production pathway and different ways that the virus disrupts this pathway. Downregulation: long line with a small line at the end; scissor shape: cleavage by protease; IF production pathway activation was indicated in two ways. Left: Activation of pathway was indicated when ssRNA or dsRNA are in the cytoplasm, in which case two adaptors (RIG1 and MDA5) recognize them, resulting in activation of IPS1 (MAVS, VISA, or cardif). IPS activates two other adaptors (IKK and TBK1) leading to phosphorylation of IRF3 and IRF7. Translocation of these adaptors to the nucleus causes ISRE promoter activation and IFN production. 2A protease has inhibitory effects in this pathway with cleavage of MDA5 and IPS1, but 3C protease downregulates RIG1 through interaction. Right: Activation of pathway is observed when ssRNA or dsRNA are in the endosome. In this situation, TLR3 and TLR7/8 are responsible for RNA recognition, resulting in the activation of two adaptors (TRIF and MYD88). TRIF activates other adaptors such as TRAF3, IKK, and TBK1 giving rise to the activation of IRF7 and IRF3, where translocation of these proteins to the nucleus causes IFN production. MYD88 also activates some other adaptors including IRAK1, IRAK4, and TRAF6 leading to phosphorylation and activation of IRF7 and translocation to the nucleus. As can be seen, 3C protease affects this pathway by cleaving IRF7 and preventing its translocation to the nucleus

which consists of histidine, aspartic acid, and cysteine in 2Apro, as well as histidine, glutamic acid, and cysteine in 3Cpro. 3C protease can attach to RNA thanks to the cysteine in the catalytic site which has nucleophile features.[46,47] The amino acid compositions P4, P2, P1, P1′, and P2′ are important for specific protease cleavage.[46,48] For 2A protease, the P1′ position is very important, which is mostly glycine. After P1′, P2 position is very important which is usually recognized by threonine and asparagine. It is followed by P2′ which can be proline, alanine, and phenylalanine, and P4, which is mostly a position for leucine or threonine. For $3C^{pro}$, P1 and P1′ positions indicate the highest conservation in the substrate sequence. The current amino acid in these positions is glutamine or glutamate for P1, as well as glycine, asparagine, or serine for P1′. In addition, the most common amino acid in positions P4 and P2′ is alanin and prolin, respectively. In both 2Apro and 3Cpro, the glycine amino acid in position P1′ is highly conserved, but 3C is mostly identified by cleavage in the Gln/Gly amino acid pair.[48,49] 3Cpro has been considered as a good target for antiviral drugs as the enteroviral polyprotein has several cleavage sites specifically for this protease, and it has a vital role in virus maturation. Many of the inhibitors are small molecules occupying the active site of the proteases.[50] One example is pyrazole compounds which inhibit 3Cpro from different enteroviruses and coronavirus protease which is similar to 3Cpro.[51] Another example is microcyclic inhibitors against enterovirus 3Cpro, norovirus, and SARS-coronavirus protease.[52] To date, rupintrivir (AG7088) and AG7404 as its analog have entered clinical trials.[53-55] Recently, researchers have been mostly focusing on rupintrivir as it proved to be potentially effective against EV71, CAV16, and EV68.[56-59]

4 | VIRAL PROTEASES AGAINST CELLULAR PROTEINS

Type I interferon is a common cytokine expressed in response to viral infections. This cytokine is the first defense line against viral infections in cells.[60] On the other hand, several viruses including influenza A, hepatitis C, dengue virus, and respiratory syncytial virus have different strategies against the host defense system resulting in infection.[61] PCR microarray indicates that there is a different response to EV71 and CA16 infection in IFN signaling pathway genes. Only a few genes after EV71 infection have overexpression, and most of the genes such as ISGs show downregulation in their expression. However, in CA16 infection, most of the genes show increased expression under the IFN induction. This evidence demonstrates that EV71 shows greater resistance to the negative effects of IFN compared to CA16.[62] Enterovirus 71 does not induce expression of IFNI, ISG54, ISG56, and tumor necrosis factor α (TNFα) following infection.[38] Viral proteases (2A and 3C) are responsible for the cleavage of viral polyprotein and virus maturation. Yet, several reports have revealed that some cellular proteins are also cleaved. For example, it was reported that 2A protease cleaves eIF4GI and poly A binding protein (PABP).[63-65] 3C can also cleave some cellular transcription factors or modulators such as TATA box binding protein, P53, histone H3, and DNA polymerase III,[66-71] where with cleavage of this transcriptional protein, DNA-dependent transcription is impaired.[72] It was reported that 3C can enter the nucleus through its precursor 3CD which contains nuclear localization site.[73,74] Hence, it can target the nuclear called named CstF-64, an essential factor for polyadenylation of mRNA in the nucleus, which is crucial in the maturation of mRNA.[75] Further, 3C of EV71 can cause apoptosis in epithelial, neuronal, and lymphocyte cells[10,76-78] and can interact with PIN2/TERF1-interacting telomerase inhibitor 1 (Pinx-1) which is an inhibitor of telomerase and tumor suppressor factor and induces apoptosis.[79] EV71 infection can prompt degradation of Trim 38 and also induce autophagy in host cells. In this regard, Song et al reported that EV71 infection suppresses TLR7 signaling pathway by inducing autophagy in infected cells, where autophagy will promote endosomal degradation and inhibit TLR7 signaling pathway.[80,81] EV71 proteases 2A and 3C are also responsible for inhibition of the cellular endoplasmic reticulum-associated degradation (ERAD) pathway.[82] Inhibition of NFkB activation by EV71 infection was reported through target transforming growth factor beta-activated kinase 1 (TAK1) and TGF-beta-activated kinase 1 (TAB) complex as TAK1/TAB1/TAB2/TAB3, cleaved by 3Cpro.[83]

5 | VIRAL PROTEASES DISRUPT INTERFERON PATHWAYS

Viruses have different evolutionary strategies to fight the host antiviral defense, which can be categorized in two groups. Firstly, they suppress IFN production through inactivation of the transcription factor by target adaptors such as IRF3/IRF7, nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) or ATF-2/C-Jun. Secondly, they suppress IFN signaling pathway activation and ISGs activation by blocking JAK-STAT signaling pathway.[84,85] Reports indicate that unlike other viruses, EV71 does not induce expression of antiviral genes in mammalian cells. EV71 suppresses IFN signaling pathway by interrupting the RIG1-IPSI formation, and with translocation of IRF3 to the nucleus using 3C protease.[38] RIG1, MDA5, and TLR3 have a crucial role in the defense against picornavirus infection.[37] EV71 infection indicates more resistance to IFN compared to CA16. Almost all of the ISGs activated by IFN will diminish in the cells that are infected by EV71, but in CA16 infection, these ISGs remain high. EV71 also decreases STAT1 and 2 phosphorylation, which has been observed less in CA16 infection.[62] Interestingly, the members of picornaviridae affect RIG1 or MDA5 by different methods, where poliovirus and encephalomyocarditis virus target both RIG1 and MDA5, but rhinovirus and echovirus only inhibit RIG1.[86-88] RIG1 is mostly seen in an inactive form with a caspase activation and recruitment domain (CARD) region, which is subject to the interaction with downstream adaptors.[38] Probably, 3C attaches to RIG1 and locks this protein in inactive form or interact with CARD region and inhibit RIG1-IPS1 interaction.[38] Chen et al also reported that EV71 infection causes ubiquitination inhibition of RIG1, resulting in induction of IFN and ISG expression.[89] Some studies have report that 3C can degrade RIG1 by its protease activity,[87,88] but others have not confirmed it.[38] EV71 3C can overcome IFN production through cleavage of IRF7 in TLR3 pathway. This cleavage is not sensitive to caspases, proteases, endocytosis, and autophagy, but sensitive to 3C inhibitors. Also, IRF7 has a cleavage site for 3C. These pieces of evidence approve the role of 3C in IRF7 cleavage.[37] A study has reported 3C cleave adaptor TRIF as a key factor in the IFN signaling pathway in rhabdomyosarcoma (RD) cell but not in HT-29 cell.[27] This study demonstrates that the cell type has an important role in protein-protein interactions between the virus and host. $2A^{pro}$ can also target mitochondrial antiviral-signaling protein (MAVS) and inhibit IFN production in Hela cells.[90] It can also cleave MDA5 which suppresses activation of IRF3.[90,91] It was reported that MDA5, which is responsible for recognizing picornaviral RNA, degraded during polivirus infection[86] and EV71 infection,[91] but in a different way. This degradation is mediated by caspase and proteasome in poliovirus infection, but in EV71 infection, this degradation occurs through 2A protease.[86,90] Other enteroviruses such as human rhinovirus 16 and echovirus 1 do not degrade MDA5.[86] RIG1 has also been a target for other enteroviruses such as poliovirus, echovirus, and HRV16 mostly through $3C^{pro}$.[87] As mentioned earlier, downstream adaptors such as MAVS are targeted by different enteroviruses including human rhinovirus 1A (HRV1A),[92] coxsackivirus B3 (by 3C protease),[93] and EV71 (by 2A protease).[85] In HRV1A, both proteases are responsible for cleavage in collaboration with caspase 3.[92] Disruption of IFN production by EV71 infection has been indicated in Figure 1. 2A protease can disrupt IFN signaling pathway by targeting one subunit of the interferon receptor called IFNR1. It cannot directly cleave IFNR1, but downregulation occurs via indirect interaction between 2A, IFNR1, and other unknown molecules.[94] Experiments suggest that this fall in IFNR1 level is related to protease activity of 2A, since by creating a mutation in cys110 and changing it to Ala110 at the catalytic site, this process will be inactivated.[94] Some viruses inhibit activation of the Jak-stat pathway by suppressing phosphorylation of STAT1 and STAT2. Also, EV71 decreases the phosphorylation level of STAT1 and STAT2 during

12 hours after infection.[95] Liu et al indicated that infection by EV71 also blocks JAK1 and TYK2 phosphorylation, yet this report did not prove changes in IFNR expression level.[95] This study suggests that 2A and 3C protease do not have an important role in the inhibition of STAT phosphorylation. Possibly, interaction of two or more viral proteins inhibits IFN signaling pathway. Furthermore, EV71 could downregulate JAK1 by inhibiting nucleocytoplasmic translocation or translation of its mRNA or by other independent proteases or via lysosomal outophagy. The reason is that JAK1 mRNA does not show a reduction after EV71 infection, but its protein is reduced.[95] 3C protease of EV71 can also suppress IFN signaling pathway through cleavage of IRF9 and inhibiting IFN signaling cascade.[96] Disruption of the IFN signaling pathway by EV71 infection has been illustrated in Figure 2.

6 | NEW MECHANISM FOR IFN SIGNALING PATHWAY SUPPRESSION

Wang et al suggested a new mechanism for IFN signaling pathway suppression. It showed that EV71 does not block phosphorylation of STAT1 and 2; rather, it inhibits the translocation of phosphorylated STAT to the nucleus, and decreases the formation of STAT1/KPNA1. It also downregulates KPNA 1 expression as a receptor for nuclear localization signal of P-STAT1. Usage of caspase inhibitors and siRNA for caspase 3 suggested that KPNA1 downregulation occurs in a caspase 3-dependent way, which results in decreased ISGs expression. 2A and 3C proteases do not cause KPNA1 degradation, interferon-sensitive response element (ISRE) activation inhibition, or ISG transcription suppression induced by IFN-β.[97] KPNA1 is one of the members of KPNA family, consisting of five types including 1α, 2α, 3α, 4α, and 5α. The role of KPNA1 in IFN signaling pathway has been investigated in some studies. This protein is effective in nuclear/cytoplasmic trafficking, directly interacts with phosphorylated STAT1, and facilitates its translocation into the nucleus.[98,99] Different viruses such as foot and mouth disease virus (FMDV) by 3C protease and Ebola virus by VP24 proteins interact with KPNA and suppress it.[100,101] VP24 has been recognized as a receptor site for nuclear localization signal on KPNA, which is crucial for translocation of P-STAT1 into the nucleus, with VP24 competing with P-STAT1 for attachment to KPNA.[102] Other viruses such as SARS Cov and porcine reproductive and respiratory syndrome virus (PRRSV) also interact with KPNA and suppress its function.[103,104] Interestingly, KPNA degradation was seen in RD, Hela, and Vero cells, but not in human gastrointestinal epithelial cells.[97]

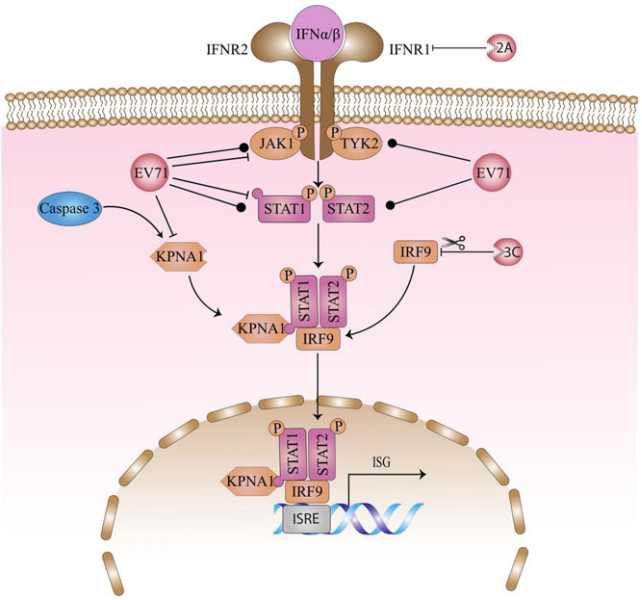

FIGURE 2 IFN signaling pathway and different ways that the virus interferes with this pathway. Downregulation: the long line with a small line at the end; inhibition of phosphorylation: the long line with a black circle at the end; scissor shape: cleavage by protease; EV71: enterovirus 71 infection. Attachment of IFN type 1 to IFNR1 and IFNR2 results in phosphorylation and activation of two adaptors called JNK1 and TYK2. The phosphorylation of these two proteins causes activation of STAT1 and STAT2 adaptors which form a complex with IRF9 and KPNA1, with the complex being called ISGF3. As can be seen in this image, STAT1 has a residue (a nuclear localization signal) which is recognized by KPNA1. This attachment induces translocation of ISGF3 to the nucleus and induces ISG's promoter. 2A protease can suppress the pathway by interacting with IFNR1, and 3C protease can cleave IRF9 and inhibit formation of ISGF3. EV71 infection can also inhibit phosphorylation of JNK1, TYK2, STAT1, and STAT2 which has been suggested in some studies. One of the latest reports found new mechanisms through which EV71 infection causes downregulation of KPNA1 in a caspase 3-dependent manner and inhibits translocation of ISGF3 to nucleus

7 | SUMMARY

Enterovirus 71 is a major cause of HFMD and is an important concern following polio eradication, as it can cause flaccid paralysis. EV71 outbreak has been reported from different countries especially in Asia.[38] As with other viruses, EV71 has some weapons to fight against the innate immune system. Some studies have reported that EV71 poorly induces IFN in infected cells, and pretreatment of cells with IFN should be performed by a high dose to protect cells from infection.[27,38] In contrast, EV71 infection in HT-29 cells can induce IFN well comparable to RD and Hella cells. TLR3 in infected RD cells remain unchanged, but in human colorectal adenocarcinoma cell (HT-29 cells), 2-to-6 fold increase was seen in TLR3 transcription 36 hours after infection.[27] This increment is probably a result of IFN induction in these cells. Possibly because of this reason, mild gastrointestinal symptoms are seen in patients infected with EV71. These pieces of evidence revealed that different cells and tissues have different responses to EV71 infection. For example, TRIF in IFN production pathway significantly declines during the first 12 hours after infection in RD cells and is rarely seen in 36 hours after infection. However, TRIF levels remain constant after infection in HT-29 cells.[27] Also, IRF7 significantly diminished after first 24 hours of infection in RD cells and was not seen 36 hours after infection. However, in HT-29 cells, IRF7 reduction is very marginal at 36 hours following infection, but 24 hours after infection, there is no change in IRF7 levels.[27] EV71 can also reduce IFN production by targeting some PRRs such as RIG1. The 3C of virus interacts with RIG1 and blocks the pathway, yet this event is not related to protease activity of 3C. However, the 3C of some enteroviruses such as poliovirus, echovirus, and rhinovirus degrade RIG1 via cleavage.[38,105] 3C can cleave IRF7 and TRIF thus causing inhibition of IFN production. This cleavage

happens at Q189-S190 and Q312-S313 positions, respectively.[37,105] 2A protease can also target MAVS and MDA5 and degrade them in Hella cells, culminating in inhibition of IFN production.[27] Nevertheless, some studies have reported that a number of enteroviruses including HRV1A cleave MAVS in a caspase-dependent manner.[90] As a second strategy, EV71 acts against the host innate immune system by affecting IFN signaling pathway. Lu et al reported that 2A protease causes decrement in IFNR1 level and suppresses IFN signaling pathway 6 hours following infection.[94] Nevertheless, Liu et al indicated that there is no change in the level of IFNR after EV71 infection. They also found that EV71 infection blocks JAK1 and TYK2 phosphorylation through downregulation of JAK1. There was no change in JAK1 mRNA levels, but reduction in the protein level was observable.[95] This study hypothesized that possibly the interaction of two or more viral proteins is responsible for that not only 2A or 3C. 3C protease of EV71 is also responsible for cleavage of IRF9, an important adaptor in the IFN signaling pathway which inhibits activation of ISRE promoter.[96] However, Wang et al suggested a new mechanism for the IFN signaling pathway suppression and rejected all of the previous mechanisms. This study suggests that EV71 does not suppress phosphorylation of STAT1 or downregulate IFNR1 and JAK1 significantly, but inhibit its translocation to the nucleus by disrupting the interaction between P-STAT1 and KPNA1 through degradation of KPNA1.[44] As mentioned earlier, IFN production happened in the HT-29 cell rather than occurring in other cells such as RD and Hella, which is in accordance with the fact that the IFN signaling pathway is active in gastric epithelial cells despite EV71 infection. Possibly, due to this event, patients do not have gastric signs or at least have mild signs. Wang et al revealed that KPNA1 degradation does not happen in gastric epithelial cells. This study proves that neither 2A nor 3C degraded KPNA1. This degradation happened through a caspase 3-dependent manner as with some other enteroviruses such as poliovirus.[44] These findings suggest that the viral protein and host protein interaction is a complex concept which is mediated by different factors such as the cell and tissue type, host immune system, and different hosts. Further evaluation of different cell types may result in new findings about the interaction between EV71 proteases and IFN signaling and production pathway. It will also be valuable to focus on the role of other viral proteins in IFN inhibition pathways. These studies suggest that viral-host protein interaction is a multifactorial concept and need further work and research to understand it more comprehensively.

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CONFLICT OF INTEREST

The authors have no competing interest.

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