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HIGHLIGHTS

REVIEW

Innate immune evasion by picornaviruses

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The family *Picornaviridae* comprises a large number of viruses that cause disease in broad spectrum of hosts, which have posed serious public health concerns worldwide and led to significant economic burden. A comprehensive understanding of the virus-host interactions during picornavirus infections will help to prevent and cure these diseases. Upon picornavirus infection, host pathogen recognition receptors (PRRs) sense viral RNA to activate host innate immune responses. The activated PRRs initiate signal transduction through a series of adaptor proteins, which leads to activation of several kinases and transcription factors, and contributes to the consequent expression of interferons (IFNs), IFN-inducible antiviral genes, as well as various inflammatory cytokines and chemokines. In contrast, to maintain viral replication and spread, picornaviruses have evolved several elegant strategies to block innate immune signaling and hinder host antiviral response. In this review, we will summarize the recent progress of how the members of family *Picornaviridae* counteract host immune response through evasion of PRRs detection, blocking activation of adaptor molecules and kinases, disrupting transcription factors, as well as counteraction of antiviral restriction factors. Such knowledge of immune evasion will help us better understand the pathogenesis of picornaviruses, and provide insights into developing antiviral strategies and improvement of vaccines.

Keywords: Immune evasion · innate immunity · interferon · picornavirus · signal transduction

Introduction

The family *Picornaviridae* comprises a variety of RNA viruses, many of which are important pathogens of human and livestock, affecting the CNS, liver, heart, and the respiratory and gastrointestinal tracts (Table 1) [1]. All members of the family *Picornaviridae* are nonenveloped, single, positive-stranded RNA viruses with genomes ranging from 7 kb to 10 kb, which consists (from 5' to 3') of a 5' untranslated region (UTR), a single open-reading frame (ORF), a 3'UTR, as well as a poly(A) tail. The single long ORF encodes a polyprotein, which is processed by viral proteases into structural proteins (VP1, VP2, VP3, and VP4) and nonstructural proteins (2A, 2B, 2C, 3A, 3B, $3C^{pro}$, and $3D^{pol}$, and in some genera, also containing L^{pro}) [2]. Structural proteins play a central role in viral capsids assembly, whereas nonstructural proteins are involved in cleavage of viral polyprotein, viral replication, translation, hijacking host-cell machinery, and multiple processes [3].

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Table 1. The diseases in humans and animals caused by picornaviruses

Full names of picornaviruses	Abbreviations	Host species	Diseases caused by the virus
Hepatitis A virus	HAV	Humans	Hepatitis A
Poliovirus	PV	Humans, cattle, swine	Poliomyelitis (Paralysis, Meningitis, Paresthesia)
Coxsackievirus A6	CVA6	Humans,	Hand, foot, and mouth disease
Human Rhinovirus	HRV	Humans	Common cold, ear infections, and infections of the sinuses
Encephalomyocarditis virus	EMCV	Humans, small rodents, pigs	Myocarditis and encephalitis
Theiler's Murine Encephalomyelitis Virus	TMEV	Mouse	Chronic demyelinating disorder, and demyelinating disease of the central nervous system
Saffold virus	SAFV	Humans	Chronic inflammation in the brains, lymphocytic pleocytosis
Enterovirus 71	EV71	Humans,	Hand-foot-and-mouth disease
Human Parechovirus	HPev	Humans,	Gastroenteritis and respiratory infections, neurological disease
Ljungan virus	LV	Humans,	Type-1 diabetes mellitus, myocarditis, and Guillain–Barré syndrome
Equine rhinitis A virus	ERAV	Horses	Equine respiratory illness
Equine rhinitis B virus	ERBV	Horses	Slight pyrexia and mild respiratory signs
Avian encephalomyelitis virus	AEV	Avian	Avian encephalomyelitis
Porcine sapelovirus	PSV	Swine	Diarrhea, pneumonia, polioencephalomyelitis, and reproductive disorders
Aichi virus	AiV	Humans	Gastroenteritis
Foot-and-mouth disease virus	FMDV	Cattle, swine and other cloven hoofed animals	Foot-and-mouth disease
Senecavirus A	SVA	Swine	Vesicular disease and mortality
Swine vesicular disease virus	SVDV	Swine	Swine vesicular disease
Porcine teschovirus	PTV	Domestic pigs and wild relatives	Teschen disease and Talfan disease

The innate immune system is the first line of host defense against pathogen infections. To elicit an antiviral state and activate the cellular antiviral immune system, the host pathogen recognition receptors (PRRs) must first sense microbial pathogens. Following ligand binding, the PPRs become activated and initiate signaling cascades through recruitment of a series of adaptor proteins such as mitochondrial antiviral signaling protein (MAVS, also known VISA, IPS-1, or Cardif) and stimulator of interferon genes (STING). The induced signaling cascade subsequently leads to the activation of transcription factors, such as interferon regulatory factors (IRF) and the NF-κB, that induce the production of IFNs. The secreted IFNs then activate inflammatory cytokines, chemokines, and antiviral proteins expression in a paracrine and autocrine manner to elicit an antiviral state. Despite strong immune regulation in cells, virus-host coevolution has led viruses to the acquisition of various strategies to circumvent innate immune recognition and antiviral responses. Viral proteins can shut down host protein synthesis, interfere with the sensing of viral elements by PRRs, and disrupt the innate immune pathway signaling to maintain robust levels of viral replication in the host and facilitate viral infection [4]. Innate immune recognition is critical for the activation of antigen-specific adaptive immune responses. A large amount of cells involved in host innate immune response secrete cytokines or interact with other cells to elicit long-lasting adaptive immune response [5, 6]. Therefore, the virus-induced inhibition on the early-stage innate immunity results in the delayed and attenuated adaptive immunity. The consequences of immune evasion on the immune responses by viruses include noncytocidal infection, infection of nonpermissive, resting or undifferentiated cells, infection with restricted viral gene expression by destruction of immune cells, downregulation of MHC-antigen expression, production of nonneutralizing antibodies, and immunologic tolerance [7]. After picornavirus infection, antibody production is important to control viral viremic spread within the infected host, and therefore, to alleviate the severity of the disease [8]. Picornaviral genes/proteins subvert signaling pathways in host cells to block the production of various cytokines and antiviral proteins, which subsequently inhibits the prompt

initiation of adaptive immune response and leads to efficient replication of the virus, contribute to the pathogenesis of the infections and related diseases (also including chronic infection and failure of vaccination under certain conditions).

Picornaviruses induce a number of diseases ranging from acute, fatal paralysis to mild respiratory disease, as well as asymptomatic infections in many hosts. Currently, there are no approved drugs for the treatment of the diseases caused by picornavirus infections. Therefore, understanding the pathogenesis of how picornaviruses evade and interfere with host cell processes might provide new insights into prevention and treatment of viral infections. In this review, we summarize the recent progress describing the evasion of the host innate immunity by picornaviruses, including evasion of PRRs recognition, disruption of adaptor molecules and their kinases, inhibition of transcription factor activation, as well as counteraction of antiviral effectors (Table 2).

Evasion of RIG-I-like receptors

The initiation of the innate immune response depends on the recognition of diverse but highly conserved components of pathogens, known as pathogen-associated molecular patterns (PAMPs), by PRRs. PRRs are mainly expressed by innate immunity cells, such as DCs, macrophages, monocytes, neutrophils, and epithelial cells. PRRs have TLRs, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs). The RLR family contains three immune sensors: retinoic acid-inducible protein I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). RLRs sense RNA virus infections to initiate and modulate antiviral immunity [9]. Despite RIG-I and MDA5 have high sequence similarity and structural homology, they play nonredundant functions in antiviral immunity by recognizing overlapping but distinct subsets of viruses: RIG-I ligands include short dsRNA or ssRNA harboring 5'-triphosphate ends with regions enriched in poly-U/UC or AU sequences; while MDA5 binds internally to long dsRNA organized in higher-ordered structures with no end specificity [10]. As for LGP2, it is also significantly involved in the antiviral response against picornaviruses, its essential antiviral functions have been determined during the replicative process of different picornaviruses [11, 12]. Picornaviruses have established numerous strategies to counteract RLRs to prevent the initiation of RLRs-mediated immune signaling (Fig. 1).

MDA5 plays a vital role in recognition of enterovirus 71 (EV71) RNA and induction of type I IFN production in HeLa and RD cells. To impair MDA5-mediated antiviral response, EV71 infection induces MDA5 degradation through activation of the caspase pathways [13]. MDA5 is also degraded in poliovirus (PV)-infected cells through a proteasome- and caspase-dependent manner [14]. In addition, PV hides its viral RNA in the viral replication complex (RC) to avoid being sensed by MDA5 [15]. The coxsackievirus (CV)-A16, CV-A6, and EV68 3C proteinase ($3C^{pro}$) blocks MDA5-triggered type I IFN induction by binding to MDA5 and inhibiting its interaction with MAVS [16]. Furthermore, MDA5 is targeted by the viral $2A^{pro}$ of CV-B3, EV71, and PV in the infected cells, which leads to the degradation of MDA5 and decreased MDA5 levels [17]. The encephalomyocarditis virus (EMCV) 2C protein and foot-and-mouth disease virus (FMDV) 2B protein interact with MDA5 to disrupt the initiation of MDA5 signaling as well [18, 19].

As for RIG-I, its degradation has been widely observed in various cells (such as HeLa and SH-SY-5Y cells) infected by PV, EV71, human rhinoviruses (HRV) types 1a and 16 (HRV1a/HRV16), echovirus type 1, CV-B3, as well as EMCV. RIG-I cleavage is mostly mediated by the viral $3C^{pro}$ both in vitro and in vivo [20-22]. In EMCV-infected cells, this degradation is also mediated by the host caspase proteinases activated during viral infection [21]. EV71 $3C^{pro}$ targets RIG-I to block subsequent recruitment of adaptor molecule MAVS and inhibit consequent nuclear translocation of IRF3 [23]. EV71 infection also inhibits the ubiquitination of RIG-I to block type I IFN production [24]. Moreover, in Senecavirus A (SVA)-infected cells, the viral proteins 2C and $3C^{pro}$ were shown to contribute to RIG-I degradation through induction of the caspase pathway signaling [25]. In FMDV-infected cells, the FMDV leader proteinase (L^{pro}), $3C^{pro}$, and 2B protein decrease RIG-I protein expression. L^{pro} and $3C^{pro}$ degrade RIG-I, however, how does 2B protein inhibit RIG-I expression remains unknown. Besides, FMDV 2B-induced decrease of RIG-I levels is considered to be specific for FMDV [26]. Furthermore, FMDV 3A inhibits the RLR-mediated IFN-β response through interacting with both RIG-I and MDA5. Meanwhile, FMDV 3A inhibits the expression of RIG-I and MDA5 by decreasing the mRNA expression [27].

LGP2, another member of the RLR family, is also involved in regulation of host antiviral effect against many kinds of picornaviruses. Mice with a disrupted LGP2 locus are more susceptible to picornaviral infections [28]. FMDV leader protease (L^{pro}) specifically interacts with and cleaves human as well as porcine LGP2. L^{pro}-induced cleavage of LGP2 remarkably subverts the type I IFN response during FMDV infection [11]. FMDV $3C^{pro}$ and 2B protein also inhibit LGP2 expression to promote viral replication. L^{pro}, $3C^{pro}$, and 2B protein target LGP2 by different strategies, having a synergy to antagonize innate immune response. L^{pro} and $3C^{pro}$ are viral proteinases that cleave many host proteins. However, 2B protein is not a proteinase, there are only RIG-I and LGP2 which have been reported to be the host proteins that were decreased by FMDV 2B protein [12, 29]. Collectively, these studies indicate that multiple viral proteins of picornaviruses are involved in disruption of RLRs functions to impair RLRs-mediated antiviral response.

Evasion of TLRs

In addition to RLRs, TLRs are involved in initiation of host innate antiviral immune response during picornavirus infection as well (Fig. 1). It has been determined that TLR3, TLR7, and TLR8 are involved in induction of host innate antiviral response during picornavirus infection in the infected epithelial cells. They are all localized into intracellular membranes, with the exception of a small proportion of TLR8 expressing at the cell surface. TLR3 recognizes dsRNA, while TLR7 and TLR8 detect ssRNA

Table 2. The antagonistic strategies utilized by various picornaviruses

Targets	Virus	Identified viral factors	Mechanism	Refs.
PRRs	PV	—	Degradation of MDA5 in a proteasome- and caspase-dependent manner	[14]
		2A	Degradation of MDA5	[17]
		$3C^{pro}$	Induction of RIG-I cleavage	[20]
	EV71	—	Degradation of MDA5 in a caspase-dependent manner	[13]
		2A	Degradation of MDA5; Decreasing TLR3 expression	[17, 31]
		$3C^{pro}$	Induction of RIG-I cleavage	[20]
		—	Disruption of TLR7 function	[39]
	EV68	$3C^{pro}$	Binding to MDA5 and inhibiting its interaction with MAVS	[16]
	HRV1a/HRV16,	$3C^{pro}$	Degradation of RIG-I	[20]
	EMCV	$3C^{pro}$	Degradation of RIG-I	[21]
	SVA	2C / $3C^{pro}$	Degradation of RIG-I	[25]
	FMDV	L^{pro}/$3C^{pro}$/2B	Degradation of LGP2;	[11, 109]
		L^{pro}/$3C^{pro}$/2B	Decreasing RIG-I protein expression	[26]
		3A	Inhibition of RIG-I, MDA5 mRNA level and interacting with RIG-I and MDA5 to disrupt signalling	[110]
	CV-A16	$3C^{pro}$	Binding to MDA5 and inhibiting its interaction with MAVS	[16]
		—	Disruption of TLR7 function	[39]
	CV-A6	$3C^{pro}$	Binding to MDA5 and inhibiting its interaction with MAVS	[16]
	CV-B3	2A	Degradation of MDA5	[17]
		—	Negatively regulation of TLR3 expression by upregulation of MiR-146a that targets TLR3	[32]
	Echovirus type 1	$3C^{pro}$	Degradation of RIG-I	[20]
Adaptor proteins and their kinases	HAV	3ABC	Cleavage of MAVS; Impairing MAVS-TBK1-IKKε complex formation	[43, 44]
		3CD	Cleavage of TRIF	[45]
		$3C^{pro}$	Cleavage of NEMO	[42]
		2B	Interfering with activities of MAVS and the TBK1/IKKε kinases	[44]
	PV	2A	Degradation of MAVS	[17]
		2C	Suppressing IKKβ phosphorylation by interaction with IKKβ	[54]
	EV71	2A	Degradation of MAVS	[47]
		$3C^{pro}$	Cleavage of TRIF; Cleavage of TAB2, TAK1, TAB1 and TAB3	[48, 50]
		2C	Interaction with IKKβ and suppresses phosphorylation of IKKβ	[53]
		—	Induction of K48-linked polyubiquitination of TRAF6 to promote proteasomal degradation of TRAF6	[51]
		—	Upregulation of the MiR-21 that targets MyD88 and IRAK1	[52]
	EV68	$3C^{pro}$	Cleavage of TRIF	[49]
		$3C^{pro}$	Cleavage of TAK1	[16]
	SVA	$3C^{pro}$	Cleavage of MAVS, TRIF, TANK; inhibiting the ubiquitination of RIG-I, TBK1, and TRAF3	[55]

(*Continued*)

Table 2. Continued

Targets	Virus	Identified viral factors	Mechanism	Refs.
	FMDV	VP3	Interaction with MAVS to disrupt mRNA level	[27]
		$3C^{pro}$	Cleavage of NEMO and TANK; Degradation of ATG5-ATG12	[57, 111]
		L^{pro}	Inhibiting the ubiquitination of RIG-I, TBK1, TRAF6, and TRAF3 to block their activation	[60]
	EMCV	$3C^{pro}$	Cleavage of TANK, and disrupting the TANK-TBK1-IKKε-IRF3 complex formation	[58, 59]
	HRV1a	$2A/3C^{pro}$	Degradation of MAVS	[61]
	CV-A16	$3C^{pro}$	Cleavage of TAK1	[16]
		2C	Suppressing IKKβ phosphorylation by interaction with IKKβ	[54]
	CV-A6	$3C^{pro}$	Cleavage of TAK1	[16]
	CV-B3	$3C^{pro}$	Cleavage of MAVS and TRIF	[46]
		2A	Cleavage of MAVS	[17]
		2C	Suppressing IKKβ phosphorylation by interaction with IKKβ	[54]
		—	Triggering MiR-146a expression that downregulates the adaptor molecule TRAF6	[32]
Transcription factors	FMDV	L^{pro}	Degradation of p65/ RelA and decrease IRF3/7 expression	[62, 63]
	PV	$3C^{pro}$	Cleavage of the C terminus of p65-RelA component	[70]
		2C	Interacting with IPT domain of p65 to inhibit the formation of p65/p50 heterodimer	[71]
	SVA	$3C^{pro}$	Cleavage of NF-κB-p65 and Poly (adpribose) polymerase, and reducing IRF3 and IRF7 protein expression level and phosphorylation	[67, 68]
	EV71,	$3C^{pro}$	Cleavage of IRF7	[112]
		2C	Interacting with IPT domain of p65 to inhibit the formation of p65/p50 heterodimer	[71]
		—	Decreasing STAT3 by upregulation of MiR-124	[77]
		—	Degradation of STAT/KANA1 in a caspase-3-dependent manner	[78]
	EV68	$3C^{pro}$	Cleavage of IRF7	[113]
		2C	Interacting with IPT domain of p65 to inhibit the formation of p65/p50 heterodimer	[71]
	CV-B1,	2C	Interacting with IPT domain of p65 to inhibit the formation of p65/p50 heterodimer	[71]
	Mengovirus	L^{pro}	Inhibiting IRF3 dimerization but not phosphorylation; Suppression of the iron-mediated NF-κB activation	[64, 65]
	TMEV	—	Disruption of the interaction between IRF3 and IFN-β gene promoter	[66]

(*Continued*)

Table 2. Continued

Targets	Virus	Identified viral factors	Mechanism	Refs.
	HRV14	—	Inhibition of phosphorylation, homodimer formation or nuclear accumulation of IRF3	[69]
		$3C^{pro}$	Cleavage of the C terminus of p65-RelA component	[70]
	Human orphan virus-1	$3C^{pro}$	Cleavage of the C terminus of p65-RelA component	[70]
JAK/STAT pathways	FMDV	$3C^{pro}$	Degradation of KPNA1 to block STAT1/STAT2 nuclear translocation	[79]
		VP3	Interacting with JAK1/2 and inhibit activation of STAT1; degrade JAK1	[80]
	EV71	2A	Decreasing the IFNAR1 level	[74, 114]
		—	Down-regulation of JAK1	[76]
		—	Degradation of KPNA1 to inhibit the p-STAT1/2 from the cytosol to the nucleus	[78]
		$3C^{pro}$	Cleavage of IRF9	[75]
	PKV	VP3	Interacting with STAT2 and IRF9 to block the formation of the STAT2-IRF9 and STAT2-STAT2 complexes	[81]
PKR	PV	—	Inducing degradation of PKR	[82, 83]
	EV71	$3C^{pro}$	Direct interaction with PKR to cleave PKR	[84]
	FMDV	$3C^{pro}$	Inducing PKR degradation through lysosomal pathway	[86]
	TMEV	L^{pro}	Preventing the interaction between viral dsRNA and PKR	[88]
2'-5'OS/RNase L system	EMCV	—	Inducing the expression of cellular protein Rnase L inhibitor (RLI) to downregulate Rnase L	[90]
	TMEV	L^*	Direct interaction with the Rnase L,	[91]
	PV	3C ORF RNA	Inhibiting the endonuclease activity of Rnase L	[93]

Note. "—" represents "unidentified."

[30]. During EV71 infection, knockdown of TLR3 in mouse and human primary immune cells impairs IFN-β production, indicating TLR3 is an important immune sensor to trigger antiviral immunity during EV71 infection. Furthermore, the EV71 protease 2A is responsible for decreasing TLR3 expression in EV71-infected cells, which impairs TLR3-mediated antiviral defenses [31]. EV71 2A decreases TLR3 expression in a manner independent of caspase- and proteasome-mediated degradation, and it directly cleaves TLR3 through its protease activity [31]. CV-B3 infection negatively regulates TLR3 expression by upregulation of microRNA (MiR)-146a which targets TLR3 mRNA, resulting in an impaired inflammatory response [32]. TLR3 also plays a key role during CV-B4 infection, and it is critical for survival of macrophages following CV-B4 infection [33]. Moreover, TLR3 is targeted by hepatitis A virus (HAV), PV, and HRV1B. An impaired TLR3 signaling has been determined in HAV-infected cells. TLR3 and MDA5, but not RIG-I, were shown to be essential for recognition of HRV1B dsRNA in bronchial epithelial cells, suggesting a vital role of TLR3 [34, 35]. Although it seems that TLR3 plays an important role during CV-B4, PV, HAV, and HRV1B infections, the immune evasion mechanisms directly targeting TLR3 in CV-B4-, PV-, HAV-, or HRV1B-infected cells remain unknown. Elucidation of the mechanism and identification of the viral proteins that interact with or disrupt TLR3 functions should be investigated in the future.

Human parechovirus 1 (HPeV-1) is sensed by TLR7 and TLR8, leading to a series of signaling cascades and synthesis of proinflammatory cytokines [36]. In lung epithelial cells, the combined recognition of HRV-6 by different TLRs (TLR2, TLR7, and TLR8) and MDA5 contributes to an overzealous proinflammatory response [37]. Despite the involvement of TLR3 and TLR8 in sensing, the viral proteins involved in HPeV-1 and HRV-6 mediated antagonistic mechanisms against these TLRs have not been determined. A possible broad inhibitory pathway to TLR7 and TLR8 sensing was suggested to be through ss oligonucleotides (ssON). Mammalian cells contain ssON that are in different size. The ssON composed of at least 25 bases have the inhibitory effect on TLRs sensing [38]. Upon dsRNA transfection, ssON inhibits endocytic pathways used by cargo destined for TLR3/4/7 signaling through

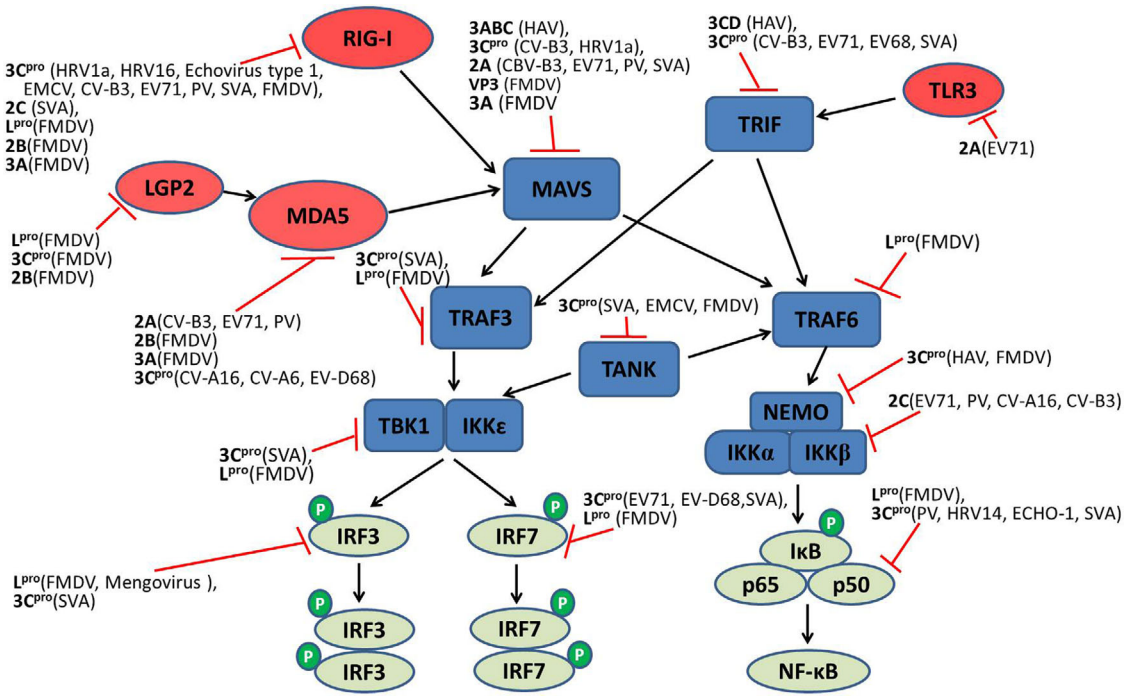

Figure 1. The identified picornaviral proteins that target the components of RLRs and TLRs pathways. The expression or activation of PRRs, including RIG-I, MDA5, LGP2, and TLR3, are inhibited by various picornaviral proteins. The innate immune signaling mediated by various adaptors, including MAVS, TRAF3, TBK1, and TRIF, TANK, TRAF6, NEMO, as well as IKKβ, are targeted by a series of picornaviral proteins to block. The activation of transcription factors IRF3 and IRF7, and the p50 subunit of the transcription factor NF-κB are antagonized by many picornaviral proteins. Red background represents PRRs, blue background represents adaptor proteins as well as their kinases, and green background represents transcription factors.

interference with clathrin-mediated endocytosis thereby dampening dsRNA-mediated immune response. However, whether ssON directly interferes with TLR3/4/7 during picornavirus infection remains unclear [38]. Further studies are required to explore the unknown mechanisms. EV71 and CV-A16 infections induce autophagy in the human bronchial epithelial cell line (16HBE cells), which promotes degradation of the endosome and its contents, causing the disruption of TLR7 function and inhibition of the TLR7-mediated IFN induction [39]. In plasmacytoid dendritic cells (pDC), FMDV is recognized by TLR7 inside the endosomal compartment, and L^{pro} has been suggested to have an antagonistic effect in pDC [40]. Together, TLRs cooperate in signaling crosstalk networks with RLRs and other sensors to initiate innate immune response and elicit the adaptive immune response during picornavirus infections. The viral factors that directly target TLRs remain largely unknown and need to be elucidated.

Disruption of adaptor proteins and their kinases

During RNA virus infection, the recognition of viral RNAs by cytosolic RLRs and TLRs triggers a signaling cascade through gradually recruiting a series of specific adaptor molecules. To block the signal transduction mediated by these adaptor molecules in the virus-infected cells, picornaviruses have developed diverse mechanisms to disrupt the recruitment process or degrade the adaptor molecules, as well as the involved kinases crucial for the signal transduction (Fig. 1).

The NF-κB essential modulator (NEMO) is a regulatory factor of I kappa kinase (IKK) complex, which is involved in NFκB pathway activation [41]. The HAV $3C^{pro}$ cleaves NEMO leading to significantly decreased production of IFN and proinflammatory cytokines and increased replication of HAV [42]. The 3ABC precursor of HAV ablates downstream signaling of the RLR pathway by cleaving MAVS, thus, inhibiting type I IFN expression and disrupting type I IFN responses. This proteolytic cleavage process are catalyzed by $3C^{pro}$ in the presence of 3A protein. The transmembrane domain in 3A directs 3ABC to mitochondria and leads to $3C^{pro}$-induced cleavage of MAVS [43]. This suggests a cooperative mechanism of picornaviral proteins to block host innate immune response. Additionally, the nonstructural proteins 2B and 3ABC of HAV cooperatively interfere with the functions of MAVS, the TANK Binding Kinase 1 (TBK1), and I kappa kinaseϵ (IKKϵ) kinases to inhibit IRF3 activation and IFN-β gene expression [44]. The 3CD protease-polymerase (a distinct viral processing intermediate) of HAV inhibits TLR3 signaling by degrading its adaptor molecule TRIF. Both the protease activity of $3C^{pro}$ and the $3D^{pol}$ sequence are essential for 3CD-induced cleavage of TRIF. While the $3D^{pol}$ polymerase activity is not related to the catalytic process, the 3D sequence is thought to promote 3CD to bind to the cleavage sites not normally recognized by $3C^{pro}$ [45]. These examples show that

the cooperative mechanisms employed by different picornaviral proteins to counteract host immune response should be considered in virus-mediated immune evasion.

Other viruses, like CV-B3, also cleave adaptor proteins. The CV-B3 $3C^{pro}$ cleaves MAVS within the proline-rich region of MAVS, leading to its relocalization. Moreover, $3C^{pro}$ localizes with TRIF to signalosome complexes and induces the cleavage of TRIF, thus, inhibiting both the type I IFN and apoptotic signaling [46]. Other studies have shown that MAVS undergoes proteolytic degradation through a caspase- and proteasome-independent manner by the $2A^{pro}$ during CV-B3 infection [17]. CV-B3 infection also triggers MiR-146a expression that subsequently downregulates the adaptor molecule TRAF6 and inhibits proinflammatory cytokine expression [32]. EV71 infection induces the degradation of MAVS as well, the viral $2A^{pro}$ cleaves MAVS which leads to its release from mitochondria resulting in decreased RLR signaling [47]. The $2A^{pro}$ of PV and EV71 also cleaves MAVS similarly, illustrating a conserved enterovirus strategy to counteract the IFN response in virus-infected cells by $2A^{pro}$. The $2A^{pro}$ of EV71 also suppresses TLR3 pathway signaling by disruption of TLR3. Furthermore, EV71 also inhibits the TLR3 signaling pathway by inducing cleavage of the adaptor molecule TRIF [48]. Interestingly, cleavage of TRIF in EV68-infected cells was shown to be mediated by $3C^{pro}$ of EV68 [49].

EV71 $3C^{pro}$ targets and catalyzes cleavage of TGF-β-activated kinase 1 (TAK1), TAK1 binding protein 1 (TAB1), TAB2 and TAB3, which significantly inhibits the activation of NF-κB pathway signaling [50]. EV71 also inhibits RLR-induced antiviral response by impairing USP4 expression and enhancing proteasomal degradation of TRAF6 [51]. Furthermore, EV71 was shown to induce MiR-21 to target MyD88 and IRAK1 to negatively regulate TLR signaling and type I IFN expression [52]. EV71 2C interacts with IKKβ to suppress the phosphorylation of IKKβ, thus, blocking NF-κB activation [53]. The involved mechanism might be that 2C forms a complex with the protein phosphatase 1 (PP1) and IKKβ to prevent its phosphorylation and maintain it in an inactive state, therefore, suppressing NF-κB activation [54]. It confirms that multiple viral proteins are involved in immune evasion during EV71 infection. Similar as 2C protein of EV71, the 2C proteins of PV, CV-A16, and CV-B3 also suppress IKKβ phosphorylation through a mechanism involving PP1 [54]. $3C^{pro}$ of CV-A16, CV-A6, and EV68 all cleave TAK1 to inhibit NF-κB pathway signaling and subvert host innate immune responses [16]. These studies suggest enterovirus target multiple steps and components of TLR and RLR signaling pathways to block host innate immune response.

In SVA-infected cells, $3C^{pro}$ interacts with MAVS, TRIF, and TANK to cleave these adaptors, leading to inhibition of TLR3- and RLRs-mediated IFNs production [55]. Moreover, SVA $3C^{pro}$ has deubiquitinating activity which it uses to reduce the ubiquitination of RIG-I, TBK1, and TRAF3, thereby blocking the signal transduction cascade [56]. For FMDV, VP3 interacts with MAVS to prevent MDA5/RIG-I-MAVS complex formation. In addition, it decreases MAVS expression by disrupting its mRNA, thus, reflecting a dual function of VP3 to suppress IFN-β production [27]. Furthermore, several roles for FMDV $3C^{pro}$ in antiviral immunity have been reported. FMDV $3C^{pro}$ was shown to cleave NEMO at the Gln 383 residue to impair NEMO-mediated IFN signaling. Moreover, $3C^{pro}$ was also shown to suppress NF-κB and IRF3 signaling through degradation of ATG5-ATG12 by $3C^{pro}$, thereby, resulting in innate immune evasion and increased viral yields [57]. EMCV $3C^{pro}$ was also shown to induce the cleavage of TANK to promote TRAF6-mediated NF-κB signaling [58]. This may partially explain why NF-κB is highly activated during EMCV infection. The cleavage of TANK was also shown to disrupt the formation of the TANK-TBK1-IKKε-IRF3 complex, therefore, inhibiting type I IFN expression as well [59]. Interestingly, Lb^{pro} of FMDV (a shorter form of L^{pro}) was shown to have a deubiquitinating activity, which inhibits the ubiquitination of RIG-I, TBK1, TRAF6, and TRAF3, leading to decreased secretion of type I IFN [60]. In HRV1a-infected cells, MAVS is degraded by not only viral $2A^{pro}$ and $3C^{pro}$ but also virus infection-activated caspase-3 [61]. These studies indicate picornaviruses directly target the adaptor molecules or indirectly manipulate the cellular intrinsic system to block TLR- and RLR-triggered signaling cascades.

Targeting the transcription factors in innate immune pathways

The members of the IRF family, the signal transducer and activator of transcription (STAT) families, and the NF-κB family modulate IFNs, proinflammatory cytokines as well as IFN-stimulated genes (ISGs) expression and therefore are widely targeted by various picornaviral proteins (Fig. 2). FMDV L^{pro} interferes with host innate immune antiviral response by reducing mRNA expression levels of IFN-β and ISGs. In FMDV-infected cells, L^{pro} directly induce the degradation of p65/RelA (subunit of NF-κB), thus, affecting the NF-κB activity and resulting in decrease expression of IFN-β and other inflammatory cytokines [62]. Moreover, FMDV L^{pro} also directly decreases IRF3 and IRF7 expression to impair dsRNA-induced IFN-α/β expression [63]. Like FMDV, EV71 and EV68 also target and induce the cleavage of IRF7 (62, 63). EV71 $3C^{pro}$ cleaves IRF7 at the constitutive activation domain of IRF7, resulting in the loss function of IRF7 and decreased IFN production [63]. The L^{pro} of mengovirus also interferes with IRF3 by inhibiting IRF3 dimerization [64]. The L^{pro} activity of mengovirus is also directly involved in suppression of NF-κB activation and thereby inhibits IFN-α/β expression in virus-infected cell [65]. Other picornavirus L^{pro} was shown to target transcription factors as well. TMEV, from the same genus as mengovirus, also disrupts IFN-β gene transcription by disruption of the interaction between IRF3 and the IFN-β gene promoter [66]. Therefore, picornaviral L^{pro} uses diverse strategies to target IRFs or NF-κB functions to benefit viral replication. Other viral factors targeting these transcription factors have also been reported. In SVA-infected cells, SVA $3C^{pro}$ expression cleaves p65 and a nuclear enzyme poly (ADP-ribose) polymerase (PARP), leading to decreased NF-κB transcriptional activity [67]. SVA $3C^{pro}$ also directly degrades IRF3 and IRF7 to inhibit ISG induction, thus, allowing the virus to

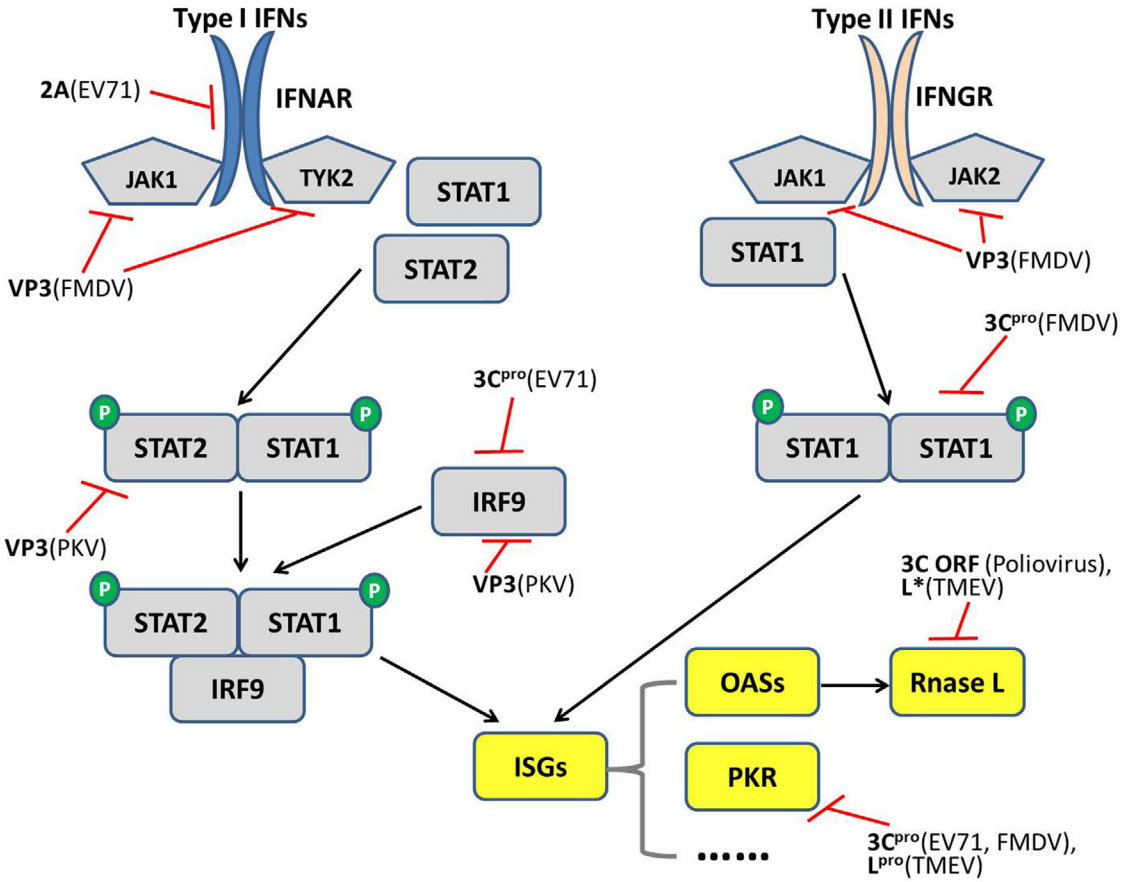

Figure 2. The identified picornaviral proteins that target the components of JAK-STAT pathway and the IFN-inducible antiviral factors. The type I IFN receptor IFNAR, the components of JAK-STAT pathway, including JAK1, JAK2, TYK2, STAT1, STAT2, and IRF9, and the ISGs containing PKR as well as Rnase L are targeted by various picornaviral proteins to impair host antiviral response. Grey background represents the components of JAK-STAT pathway, and yellow background represents IFN-inducible antiviral factors.

escape host antiviral response [68]. Other viruses like HRV14 also suppress the host type I IFN production by suppression of phosphorylation, dimerization, or nuclear translocation of IRF3 [69]. However, the viral proteins responsible for this effect remain unknown.

At the early stages of PV infection, IκBα is degraded and NF-κB is gradually imported into cellular nucleus to induce proinflammatory cytokine expression. However, at later stages of infection, the PV $3C^{pro}$ efficiently cleaves the C terminus of p65/RelA, which rapidly inactivates NF-κB activity and suppresses the expression of proinflammatory cytokines [70]. The cleavage of p65/RelA is also observed in cells infected by other picornaviruses such as enteric cytopathic human orphan virus, EV71, and HRV14 [70], suggesting a common antagonistic mechanism targeting the p65/RelA subunit of NF-κB. In addition, the 2C protein of PV type I, PV type II, CV-B1, EV68 all interfere with the activation of NF-κB through interacting with p65 and IKKβ, suggesting a conserved strategy in enteroviruses [71]. Despite the elucidation of many antiviral immune inhibitory processes, many picornaviral proteins that target IRF3/7 or NF-κB to limit their transcriptional ability have not been identified. More studies are required to unravel the underlying new mechanisms targeting these transcription factors. As for the members of STAT family, we will review the advances in the next section.

Targeting the canonical IFN signaling pathways

IFNs (including type I, type II, and type III IFNs) play a crucial role in the regulation and activation of host innate immune responses to viral infections, and restricting viral replication and spread. During the early phase of picornavirus infection, type I and II IFNs induce hundreds of ISGs through activation of the JAK-STAT pathways to mount an antiviral state in virus-infected cells and neighboring cells. Moreover, type I and II IFNs stimulate DC maturation to promote antigen presentation to T cells and induce a long-lasting adaptive immune response [72]. Type III IFNs also play an important antiviral function during picornavirus infection [73]. To counteract the IFN signaling pathway, many picornaviruses have evolved to encode different mechanisms to repress host IFN systems: (1) directly cleave and degrade IFN receptors or key components of the JAK-STAT pathway; (2) recruit the ubiquitin proteasome system to destabilize proteins that are essential

for the IFN response; (3) bind to and sequester crucial proteins of IFN signaling pathway to prevent activation.

In EV71-infected cells, the 2A protein induces the degradation of IFN receptor 1 (IFNAR1), thus, blocking the IFN-mediated phosphorylation of JAK1, TYK2, and STAT1 as well as STAT2, and antagonizing host IFN response [74]. Moreover, EV71 $3C^{pro}$ was shown to cleave IRF9 both in vitro and in vivo, indicating an antagonistic effect on the IRF9-mediated antiviral response [75]. EV71 infection also induces the proteasomal degradation of JAK1 to prevent the phosphorylation of JAK1 in MRC-5 and RD cells [76]. Besides, EV71 infection upregulates MiR-124 which can target STAT3. The increase of MiR-124 expression results in impaired expression of STAT3 and leads to an attenuated antiviral response [77]. Another study reported that EV71 infection inhibits the translocation of p-STAT1/2 from the cytosol to the nucleus by inhibiting the interaction between p-STAT1 and KPNA1 (karyopherin-α1, a nuclear localization signal receptor for p-STAT1) through degradation of KPNA1 through activation of caspase-3, leading to a decrease of ISGs expression and inhibition of the IFN response [78]. Therefore, many complicated mechanisms are involved in the EV71-mediated suppressive effect on the JAK-STAT pathway. As for other picornaviruses, FMDV $3C^{pro}$ was shown to degrade KPNA1 and, thus, interferes with STAT1/STAT2 nuclear accumulation and the subsequent transcription of antiviral genes [79]. FMDV VP3 interacts with JAK1/2 to block the phosphorylation, dimerization, and nuclear transportation of STAT1. FMDV VP3 also induces the degradation of JAK1 to disrupt the formation of the JAK1 complex through the lysosomal pathway [80]. In other viruses like porcine kobuvirus (PKV), VP3 was shown to associate with STAT2 and IRF9, and interfere with the assembly of the STAT2-IRF9 and STAT2-STAT2 complexes, inhibiting the nuclear transportation of the transcription factor IFN-stimulated gene factor 3 (ISGF3), and thus, inhibiting type I IFN response [81]. It is unclear whether the JAK-STAT pathway activated by type III IFN is also blocked by these picornaviruses. Further studies should be performed to study the complexity of the interplay between JAK/STAT signaling and picornavirus antiviral antagonism.

Evasion or targeting of ISGs

Virus infections activate IFN signaling pathway, leading to the transcription of hundreds of ISGs which are crucial for limiting virus infections. The ISGs, including the ds RNA activated protein kinase PKR, 2'-5'-oligoadenylate synthetases (2′, 5′-OASs), IFITs, viperin, ISG15, as well as L3HYPDH, have been reported to play important antiviral functions against several picornaviruses. We gather current advances concerning the interplay between these ISGs and various picornaviruses (Table 2 and Fig. 2).

PKR binds to dsRNA molecules generated during the viral replication, and it is an important mediator of the antiproliferative and antiviral effects utilized by IFN-α/β. Several different antagonistic mechanisms by picornaviruses targeting PKR have been determined. In PV-infected cells, PKR is highly activated and rapidly degraded by a mechanism that is independent of the viral proteases 2A or $3C^{pro}$, and it is proposed that a cellular protease activated by PV infection is responsible for the degradation of PKR [82, 83]. In EV71-infected cells, EV71 $3C^{pro}$ interacts with and cleaves PKR to abate the phosphorylation of PKR at the site proximal to the dsRNA-binding domain of PKR, which considerably diminishes PKR-mediated antiviral effect. In addition, the generated short *N*-terminal PKR fragment can be used by EV71 to enhance viral replication [84]. PKR was shown to be required for the antiviral activity in FMDV-infected porcine cells [85], and FMDV decreases PKR expression as infection progresses [86]. Further studies showed that FMDV $3C^{pro}$ causes PKR degradation through activation of cellular lysosomal pathway [87]. TMEV L^{pro} disrupts PKR function by preventing the interaction between PKR and viral dsRNA during virus infection, thus, inhibiting the consequent PKR-mediated eIF2α phosphorylation and antiviral response. Interestingly, this study found that TMEV L^{pro} did not directly interact with either dsRNA or PKR, and the exact mechanism remains unknown [88].

The 2′, 5′-OASs are IFN-induced antiviral enzymes that catalyze the ATP conversion into 2'-5'-linked oligoadenylate (2-5A) which binds to endoribonuclease RNase L. The activated RNase L cleaves ss regions of viral and cellular RNA, resulting in decreased translation and subsequently decreased protein synthesis and diminished viral replication, and ultimately causes the apoptosis of infected cells. In EMCV-infected cell lines, RNase L is shown to degrade EMCV RNA without altering the cellular RNA profile [89]. Nevertheless, RNase L is downregulated upon EMCV infection, which is due to the expression of the cellular protein RNase L inhibitor (RLI) [90]. Other picornaviruses also target the OAS/RNase L pathway such as TMEV. The *L** protein (an accessory protein of TMEV) of TMEV counteracts the IFN-inducible OAS/RNase L pathway by a direct interaction with RNase L [91]. The OAS/RNase L pathway also plays an important antiviral function against CV-B4 infection. The RNase $L^{-/-}$ mice showed significantly increased susceptibility to CV-B4 infection compared with the WT mice. RNase L is also required for an efficient IFN-α response against CV-B4 [92]. Whether there are viral proteins abrogate the OAS/RNase L pathway during CV-B4 infection remains unclear. In PV-infected cells, a unique antagonistic strategy is utilized to circumvent OAS/RNase L pathway. The RNA structure in the 3C ORF of PV suppresses the endonuclease activity of RNase L, therefore, making the PV mRNA resistant to cleavage by RNase L [93]. Whether similar RNA structures exist in the genome of other picornaviruses is unknown and should be investigated.

Ubiquitin-like protein ISG15 is rapidly induced after RNA virus infection. ISG15 directly inhibits viral replication by interaction with various viral proteins to interfere with their functions, or by ISGylation of viral proteins to limit viral trafficking and release [94]. FMDV L^{pro} cleaves ISG15 between Arg155 and the C-terminal Gly156-Gly157 sequence, which irreversibly damages the protein, thereby inhibiting the antiviral signaling [95]. Both $ISG15^{-/-}$ and $Ube1l^{-/-}$ mice are more susceptible to CV-B3 infection and upon infection suffer from more severe myocarditis, enhanced virus multiplication, and increased lethality compared to the virus-infected WT mice, suggesting that ISG15 conjugation

plays a key role in inhibiting CV-B3 infection and viral-induced disease [96]. FMDV and SVA viral proteins have been described to play antagonistic effect by inhibiting the ubiquitination of host molecules. Whether there are also some picornaviral proteins that reflect inhibitory effect on the ISGylation (ISG15 modification) of several host proteins remains unknown and should be investigated.

Recently, the newly identified ISG L3HYPDH was determined to play a role in suppression of EV71 propagation [97]. L3HYPDH is a trans-3-hydroxy-L-proline dehydratase, which specifically catalyzes the dehydration of dietary trans-3-hydroxy-L-proline and prevents proteins from degradation such as collagen IV [98]. The C-terminal region of L3HYPDH was shown to interfere with the function of international ribosome entry site (IRES) to block viral protein translation [97]. Since L3HYPDH is a newly identified antiviral effector against picornavirus. More studies should be performed to elucidate the interaction between this ISG and viral replication during picornavirus infection.

The IFN-induced protein with tetratricopeptide repeats (IFITs) family members play significant antiviral effect in various hosts. Most mammals contain four members: IFIT1 (also known as ISG56), IFIT2 (ISG54), IFIT3 (ISG60), and IFIT5 (ISG58). IFIT family members play an important role in degrading invasive RNA. Overexpression of IFIT3 substantially decreases EMCV loads in the infected cells, indicating an antiviral effect of IFIT3 against EMCV [99]. However, no effect on EMCV was observed for IFIT1 and IFIT2 [100, 101]. A reason for this evasion may be that the EMCV mRNA is not capped and that EMCV masks its viral RNA at the 5' end with a small viral protein [101]. Interestingly, FMDV 3B protein also binds to the 5'-terminus of viral genome although it is unknown whether this affects the ability of the IFITs to degrade the viral RNA [102]. The role of IFITs in picornaviruses should be investigated to uncover other viruses that have a similar immune evasion strategy as EMCV.

Viperin suppresses viral replication by blocking the synthesis or disruption of the functions of virally encoded components, inhibiting virus budding and release through disrupting lipid raft microdomains on the plasma membrane, catalyzing the production of a small molecule inhibitor of viral RNA polymerization, or directly interacting with viral proteins to interfere with their functions [103]. As for picornaviruses, viperin has been reported to be an important antiviral effector against HRV and EV71 [104, 105]. Viperin suppresses EV71 replication by a direct interaction with viral 2C protein in the ER. Whether 2C protein has a transient antagonistic effect remains unknown. Viperin expression in EV71-infected SK-N-SH cells is significantly upregulated before 24 h postinfection. While at 48 and 72 hpi, viperin level is significantly reduced [35]. This suggests that an unidentified antagonistic strategy is employed by EV71 to decrease viperin expression. The mechanisms behind viperin-induced suppression of other picornaviruses and the virus-mediated antagonistic mechanisms remain largely unknown. Further studies should be performed to explore the interplay between viperin and picornaviruses.

Conclusions and Discussion

The members of the *Picornaviridae* family utilize multiple elegant strategies to evade innate immune response. Use of the current knowledge on viral innate immune evasion is very helpful for development of novel vaccines and antivirals. Many central proteins in the antiviral immune signaling are interesting for antiviral development. As multiple viral proteins target MAVS to impair host IFN response during picornavirus infection. MAVS has been used as a tool and strategy to develop potential antivirals against picornavirus infections [106]. Many picornaviral proteins are essential for the virus-induced suppression of innate immune signaling, therefore, several picornaviral proteins have been targeted to develop antiviral drugs. The $3C^{pro}$ and L^{pro} play important roles in the life cycle of the viruses and suppression of host innate immune response. The pan-protease inhibitors targeting the $3C^{pro}$ or L^{pro} could be utilized as potential antiviral agents for the treatment of picornavirus infections. Inoculation of swine with FMDV SAP-mutant virus induces early protection against disease. FMDV SAP mutant is a recombinant virus with mutations in L^{pro} that impairs the antagonistic function of L^{pro} [107]. Therefore, mutation or deletion of the antagonistic sites in viral genome may be a strategy for improving the efficiency of picornaviral vaccines [108]. Taken together, a detailed understanding and carefully examination of the mechanisms on how picornaviruses evade host immune system will help develop new antiviral drugs for treatment of picornavirus infections, as well as high efficient vaccines for prevention of the related diseases.

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Abbreviations: **CV**: coxsackievirus · **EMCV**: encephalomyocarditis virus · **EV71**: enterovirus 71 · **FMDV**: foot-and-mouth disease virus · **HAV**: hepatitis A virus · **HPeV-1**: human parechovirus 1 · **IFNAR1**: IFN receptor 1 · **IKK**: I kappa kinase · **IRF**: interferon regulatory factors · **ISGs**: IFN-stimulated genes · **LGP2**: laboratory of genetics and physiology 2 · **MAVS**: mitochondrial antiviral signaling protein · **MDA5**: melanoma differentiation-associated gene 5 · **MiR**: microRNA · **NEMO**: NF-κB essential modulator · **ORF**: open-reading frame · **pDC**: plasmacytoid dendritic cells · **PKV**: porcine kobuvirus · **PP1**: protein phosphatase 1 · **PRRs**: pathogen recognition receptors · **PV**: poliovirus · **RIG-I**: retinoic acid-inducible protein I · **RLRs**: RIG-I-like receptors · **STAT**: signal transducer and activator of transcription · **ssON**: ss oligonucleotides · **SVA**: Senecavirus A · **TBK1**: TANK binding kinase 1 · **TAK1**: TGF-β-activated kinase 1 · **UTR**: untranslated region

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