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REVIEW

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Interplay of swine acute diarrhoea syndrome coronavirus and the host intrinsic and innate immunity

Fei Zhao^{1†}, Xiao Cong^{2†}, Xiaobo Huang¹, Yi Zheng¹, Qin Zhao¹, Yiping Wen¹, Rui Wu¹, Senyan Du¹, Sanjie Cao^{1*}, Feng Cong^{2*} and Yiping Wang^{1,3*} 

Abstract

Swine acute diarrhoea syndrome coronavirus (SADS-CoV), a novel HKU2-related coronavirus of bat origin, is a newly emerged swine enteropathogenic coronavirus that causes severe diarrhoea in piglets. SADS-CoV has a broad cell tropism with the capability to infect a wide variety of cells from human and diverse animals, which implicates its ability to hold high risks of cross-species transmission. The intracellular antiviral immunity, comprised of the intrinsic and innate immunity, represents the first line of host defence against viral infection prior to the onset of adaptive immunity. To date, there are no vaccines and drugs approved to prevent or treat SADS-CoV infection. Understanding of the mutual relationship between SADS-CoV infection and host immunity is crucial for the development of novel vaccines and drugs against SADS-CoV. Here, we review recent advancements in our understanding of the interplay between SADS-CoV infection and the host intrinsic and innate immunity. The extensive and in-depth investigation on their interactive relationship will contribute to the identification of new targets for developing intervention strategies to control SADS-CoV infection.

Keywords Swine acute diarrhoea syndrome coronavirus, SADS-CoV, intrinsic immunity, innate immunity, immune evasion

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1 Introduction

Coronaviruses are a large group of enveloped positive-sense single-stranded RNA viruses that belong to the subfamily *Coronavirinae*, family *Coronaviridae*, and order *Nidovirales* [1]. Based on the genetic properties, the *Coronavirinae* family is categorized into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* [1]. Coronavirus infection can cause mild to severe respiratory and digestive tract diseases in a wide range of wild and domesticated birds and mammals, including humans, posing a huge threat to animal and human health [1]. Currently, the known swine enteropathogenic coronaviruses that cause diarrhea in pigs include transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV), swine acute diarrhea syndrome coronavirus (SADS-CoV), and porcine deltacoronavirus (PDCoV) [2]. Among them, TGEV, PEDV, and SADS-CoV belong to the *Alphacoronavirus* genus, while PDCoV is a member in the *Deltacoronavirus* genus [3].

SADS-CoV, also known as porcine enteric alphacoronavirus (PEAV) and swine enteric alphacoronavirus (SeACoV), is a newly emerged swine enteric coronavirus that was first discovered in 2017 in the Guangdong Province, China [4–6]. SADS-CoV is a novel HKU2-related coronavirus that spills over from bat to cause severe diseases in domestic animals [4–6]. SADS-CoV causes severe vomiting, watery diarrhoea, dehydration, and high mortality rates in newborn piglets, leading to enormous economic losses in the pig industry [4–6]. Fortunately, in addition to Guangdong [4–8], SADS-CoV has been reported to cause sporadic outbreaks only in four other Provinces in China so far, including Fujian, Jiangxi, Guangxi, and Henan [9–12].

The RNA genome of SADS-CoV is approximately 27 kilobases long, which contains a 5′-untranslated region (UTR), open reading frame 1a (ORF1a), ORF1b, spike protein (S), ORF3/NS3a, envelope protein (E), membrane protein (M), nucleocapsid protein (N), NS7a, NS7b, and 3′-UTR [12, 13]. Within the 5′ two thirds of the genome, ORF1a and ORF1b encode polyprotein 1a (pp1a) and pp1b, respectively, which are cleaved by two virus-encoded proteases, papain-like protease 2 (PLP2) and 3 chymotrypsin-like protease (3CLPro), to generate 16 nonstructural proteins (NSP1–16) involved in viral replication and transcription [12, 13]. PLP2 and 3CLPro

are encoded by *NSP3* and *NSP5* genes, respectively. The remaining 3′ one third of the genome expresses four structural proteins (S, E, M and N) and three accessory proteins (ORF3/NS3a, NS7a, and NS7b) [12, 13]. The S protein consists of the S1 and S2 subunits, which mediate receptor binding and membrane fusion, respectively, to promote viral entry [14–16]. The E and M proteins are main components of viral envelop essential for viral assembly and release, and N protein typically participates in virion packaging by binding to viral genomic RNA [12, 13]. However, the functions of the three accessory proteins are largely unknown.

SADS-CoV is capable of infecting a large variety of cell lines from humans and animals, including swine, chickens, monkeys, cats, dogs, mice, rats, hamsters, mink, and bats [17–20]. Although SADS-CoV has not been reported to infect humans, its broad host tropism implicates that SADS-CoV holds a high risk of cross-species transmission and poses a potential threat to public health [21]. To gain entry into the cells, SADS-CoV is first attached to heparan sulfate and sialic acid on the target cell surfaces [16], then utilizes the S1 subunit of S protein to bind cellular receptors and the S2 subunit to trigger membrane fusion. While N-linked glycosylation of host cells plays an important role in SADS-CoV attachment [22], the specific N-linked glycoproteins mediating this process remain unknown. SADS-CoV entry requires cleavage of S protein by diverse host proteases, including furin, cathepsin L, cathepsin B, transmembrane protease serine 2 (TMPRSS2), TMPRSS4, and TMPRSS13 [14–16, 22, 23]. Furthermore, bile acids, a common type of microbial metabolites, were identified to enhance SADS-CoV entry in porcine intestinal enteroids through caveolae-mediated endocytosis [24]. However, SADS-CoV does not use the known coronavirus functional receptors, including angiotensin converting enzyme 2 (ACE2), dipeptidyl peptidase 4 (DPP4), and aminopeptidase N (APN), for cellular entry [6, 17, 18]. Though the precise mechanisms of SADS-CoV entry remain elusive, the recent generation of recombinant vesicular stomatitis virus with its G protein replaced by SADS-CoV S protein and green fluorescent protein-labelled recombinant SADS-CoV will provide a valuable platform for accelerating the identification of the functional receptors for SADS-CoV entry [15, 16].

To date, no vaccines and drugs are commercially available to defend SADS-CoV infection. Understanding the interplay between SADS-CoV and host antiviral immunity is critical for expediting the research and development of vaccines and drugs against SADS-CoV infection. Therefore, this review summarizes recent advancements in our understanding of the interplay of

SADS-CoV and the host intrinsic and innate immunity, providing new insight into the complex relationship between SADS-CoV and intracellular antiviral immunity.

2 Intrinsic versus innate immunity

Upon virus infection, intracellular antiviral immunity serves as the first line of host defense against invading viruses before the onset of adaptive immunity. Based on the requirements for the interferon (IFN) system, host intracellular antiviral immunity can be divided into two major arms: (1) intrinsic immunity (also known as cell-intrinsic or cell-autonomous immunity) and (2) innate immunity [25–30]. Intrinsic immunity refers to an IFN-independent antiviral response conferred by constitutively expressed cellular proteins that are known as intrinsic host restriction factors or intrinsic host antiviral factors (Figure 1). While these factors are typically preexistent in certain cell types, they can be further induced by viral infection. The host restriction factors restrain viral replication immediately and directly after infection, often prior to the beginning of the IFN response. However, these factors can also be upregulated by IFN, which can remarkably enhance

their antiviral activities to better inhibit viral replication. In the past decades, numerous cellular proteins have been identified as the host restriction factors, including interferon-induced transmembrane (IFITM) proteins [31–35], cholesterol 25-hydroxylase (CH25H) [36–38], interferon-inducible IFI16 protein [39–41], optineurin (OPTN) [42], and transmembrane protein 53 (TMEM53) [43], that are able to target different stages of viral life cycle for viral inhibition.

In contrast, innate immunity represents an IFN-dependent antiviral response mediated by cellular receptors that are known as pattern recognition receptors (PRR) (Figure 1). The well characterized mammalian PRR include toll-like receptors (TLR), retinoic acid-inducible gene I (RIG-I)-like receptors (RLR), the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), and the cytosolic DNA sensor stimulator of interferon genes (STING) [44]. Following the recognition of pathogen-associated molecular patterns (PAMP) of viruses (such as viral nucleic acids) by host PRR, the associated cellular signalling pathways are activated. Taking RLR signalling pathway for example, the sensors RIG-I and melanoma differentiation-associated protein

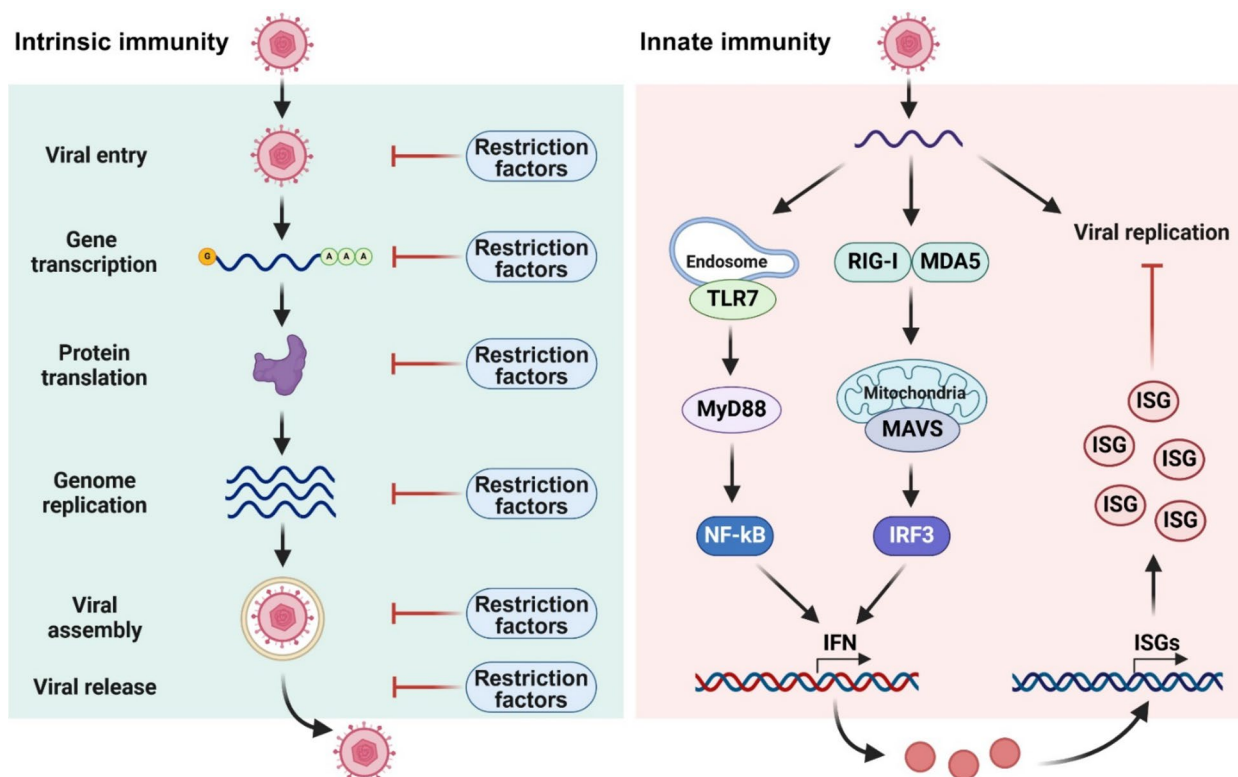


Figure 1 Intrinsic versus innate immunity. During Intrinsic immunity, the constitutively expressed host restriction factors exert antiviral activities in different stages of viral life cycle. In contrast, invading viral DNA or RNA are recognized by specific host PRR (such as TLR7, RIG-I, and MDA5) during innate immunity that signal to induce IFN secretion, which further triggers the expression of numerous ISG to restrict viral replication. Figure created with BioRender.

5 (MDA5) are activated by viral RNA, then interact with the caspase activation and recruitment domain (CARD) on mitochondrial antiviral signalling protein (MAVS), which acts as the critical adaptor protein to mediate downstream signal transduction [45, 46]. MAVS relays the signal to TANK-binding kinase 1 (TBK1) and inhibitor of nuclear factor kappa B ($\text{I}\kappa\text{B}$) kinase- ϵ (IKK ϵ) through tumour necrosis factor (TNF) receptor-activated factor 3 (TRAF3), which causes activation of the transcription factors (TF) including interferon regulatory factor (IRF3), IRF7, and nuclear factor kappa B (NF- κB) [45, 46]. Activated TF are then transported into the nucleus where they trigger transcription of the genes encoding IFN and proinflammatory cytokines [45, 46].

The IFN are classified into three different families: type I IFN (IFN α , IFN β , IFN ϵ , IFN τ , IFN κ , IFN ω , IFN δ , and IFN ζ), type II IFN (IFN γ), and type III IFN (IFN λ 1, IFN λ 2, IFN λ 3, and IFN λ 4) [26, 47]. All three types of IFN have an inherent ability to induce the expression of IFN-stimulated genes (ISG) in an autocrine and paracrine manner, which can create an antiviral cellular environment to restrict viral replication [26, 47]. The type I and type II IFN receptors, the heterodimeric IFN α receptor 1/2 (IFNAR1/IFNAR2) and IFN γ receptor 1/2 (IFNGR1/IFNGR2) complexes, respectively, are ubiquitously expressed almost in all cell types, while the expression of type III IFN receptors, the heterodimeric IFN λ receptor 1/IL10 receptor 2 (IFNLR1/IL10R2) complex, is restricted in the epithelial cells of mucosal surfaces [48]. After binding to their cognate receptors, type I and type III IFN activate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signalling pathway to generate the heterotrimeric transcription factor complex interferon-stimulated gene factor 3 (ISGF3), which is composed of phosphorylated STAT1/STAT2 heterodimers and IRF9 [47, 49]. Likewise, type II IFN also activate the JAK-STAT pathway, leading to the formation of so-called IFN γ -activated factor (GAF), which consists of phosphorylated STAT1 homodimers [47]. Activated ISGF3 and GAF are subsequently transported to the nucleus where they induce the expression of hundreds of ISG by binding their promoter elements, IFN-stimulated response elements (ISRE) and gamma-activated sequences (GAS), respectively [47].

3 Intrinsic immunity to SADS-CoV

3.1 CH25H

CH25H is a member in the redox enzyme family that is primarily located in the endoplasmic reticulum (ER) and Golgi apparatus. CH25H catalyses the oxidation of cholesterol to 25-hydroxycholesterol (25HC), which is a type of endogenous hydroxysterol that acts in cholesterol homeostasis [26, 50]. When the levels of cellular cholesterol are increased, 25HC reduces its accumulation

by suppressing the activities of sterol regulatory element-binding protein (SREBP), which induces the expression of genes associated with cholesterol biosynthesis [51]. Furthermore, 25HC promotes cholesterol trafficking into the ER [26]. Therefore, CH25H and its enzymatic product 25HC are generally thought to play essential roles in maintaining cholesterol homeostasis. However, 25HC can also participate in multiple important cellular processes, including lipid metabolism, antiviral process, inflammatory response, and cell survival [52].

CH25H is an IFN-induced enzyme that is generally upregulated in response to viral infection. It has recently been demonstrated that CH25H has a broad antiviral activity against numerous viruses through various mechanisms, such as inhibition of virus-cell fusion and regulation of membrane cholesterol [26]. SADS-CoV infection upregulates CH25H expression not only in porcine intestinal epithelial cells IPI-2I and Vero E6 cells in vitro, but also in the ileal tissues of piglets in vivo [38]. Treatment of IPI-2I cells with IFN α markedly increases CH25H expression, indicating that porcine CH25H is an ISG [38]. Consistent with the findings for other swine enteric coronaviruses PEDV, TGEV, and PDCoV [53, 54], CH25H and 25HC also inhibit SADS-CoV entry into the cells [38]. Mechanistically, both CH25H and 25HC block S protein-mediated membrane fusion, thus suppressing SADS-CoV replication (Figure 2).

3.2 TMEM53

TMEM53 is a nuclear envelope transmembrane protein that is localized in the outer membrane of the nucleus [55, 56]. The biological function of TMEM53 is largely unknown. The findings from limited studies reveal that TMEM53 regulates cell cycle in a tissue- and cell type-dependent manner and its deficiency is associated with sclerosing bone disorder [57, 58]. The antiviral activity of TMEM53 was first identified through a large-scale human cDNA library screening for potential host restriction factors against SADS-CoV [43]. Mechanistic study unveils that TMEM53 interacts with SADS-CoV NSP12 protein to disrupt NSP8-NSP12 interaction, which interferes with the formation of viral RNA-dependent RNA polymerase (RdRp) complex (Figure 2), thus inhibiting RdRp activity and viral RNA synthesis [43]. Notably, TMEM53 displays broad antiviral activities against multiple closely related bat HKU2-related coronaviruses with zoonotic potential [43]. These important findings suggest that TMEM53 may serve as a promising therapeutic target against SADS-CoV and HKU2-related coronavirus infection [43]. Because TMEM53 is a newly identified host restriction factor, the information on its antiviral activity and the underlying mechanisms is still very rare. It is therefore

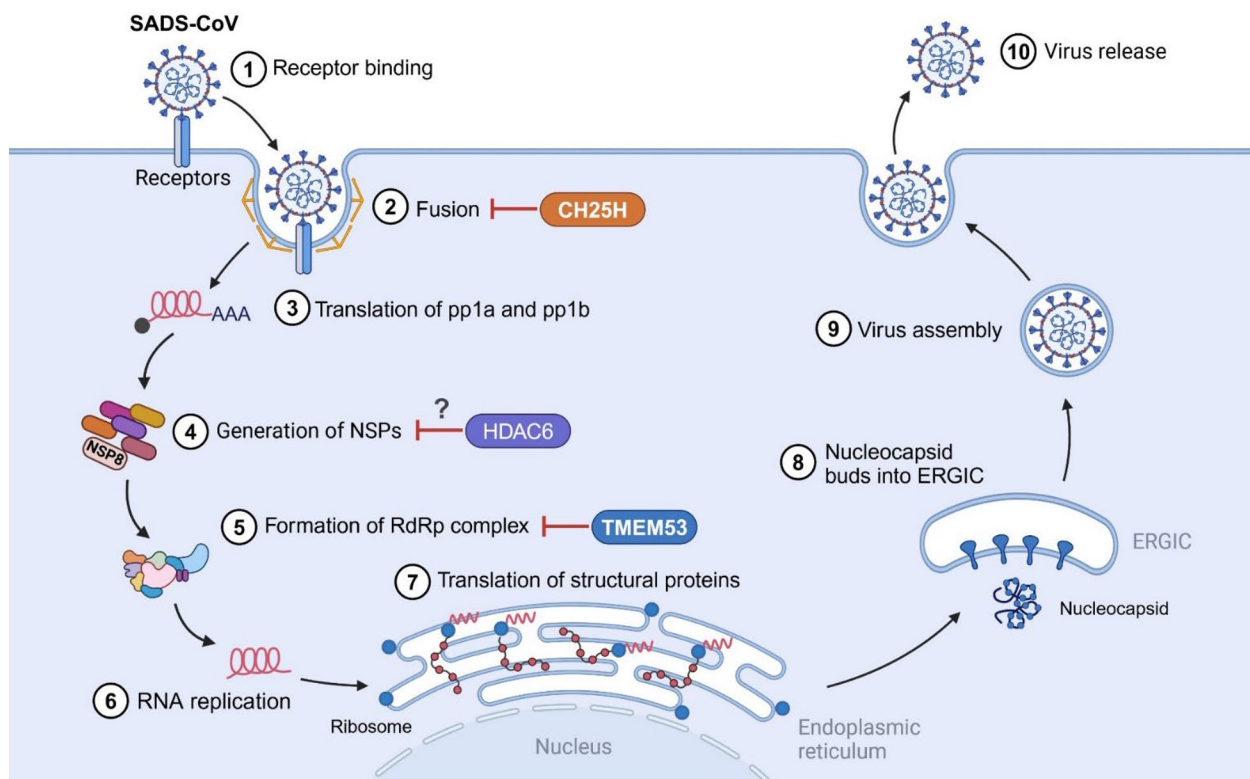


Figure 2 Intrinsic host restriction factors against SADS-CoV. The identified host restriction factors CH25H, TMEM53, and HDAC6 target different stages of SADS-CoV life cycle to inhibit viral replication: CH25H blocks S protein-mediated membrane fusion, TMEM53 disrupts the formation of viral RdRp complex, and HDAC6 might induce NSP8 degradation. Figure created with BioRender.

warranted to determine whether TMEM53 restrains the replication of other viruses, especially other swine enteric coronaviruses.

3.3 HDAC6

Histone deacetylase 6 (HDAC6) is a unique cytoplasmic deacetylase that participates in a variety of cellular processes by deacetylating nonhistone substrates [59, 60]. Apart from its deacetylase activity, HDAC6 also includes a zinc-finger ubiquitin binding domain that modulates a wide range of physiological processes by interacting with proteins followed by induction of their degradations through the ubiquitin–proteasome system [59, 60]. As a result, HDAC6 plays pivotal roles in multiple pathological processes, including neurodegenerative diseases, cancers, and viral infections [59, 60]. Indeed, HDAC6 has been demonstrated to exert antiviral activities against numerous viruses, including swine enteric coronaviruses [61–63]. HDAC6 significantly restricts the replication of all four swine enteric coronaviruses SADS-CoV, PEDV, TGEV, and PDCoV [62, 63]. While the specific mechanism by which HDAC6 inhibits the replication of SADS-CoV, PEDV, and TGEV remains unidentified, the research

on PDCoV reveals that HDAC6 interacts with PDCoV NSP8 and induces its degradation through the deacetylation at the lysine 46 (K46) and the ubiquitination at K58, thus restricting viral replication [62]. However, PDCoV NSP5 is able to cleave HDAC6 at glutamine 519 (Q519), which leads to a loss in its ability to degrade NSP8, to dampen its antiviral effect [63]. Interestingly, the NSP5 orthologs from SADS-CoV, PEDV, and TGEV also target HDAC6 at residue Q519 for cleavage, demonstrating that swine enteric coronaviruses share common strategy of NSP5-mediated cleavage to antagonize the antiviral activity of HDAC6 [63]. Future work will be needed to define whether HDAC6 also targets NSP8 orthologs from SADS-CoV, PEDV, and TGEV for proteasomal degradation to restrain viral replication (Figure 2).

4 Innate immunity to SADS-CoV

4.1 Type I and type III IFN inhibit SADS-CoV

Type I and type III IFN are the most critical effector molecules in the host antiviral innate immunity. Although SADS-CoV infection fails to induce IFN β and IFN λ production robustly [64, 65], pretreatment of cells with IFN α , IFN δ , and IFN λ 3 can effectively

inhibit SADS-CoV replication [66–68]. Interestingly, IFN α -mediated inhibition of SADS-CoV replication is dependent on the expression of the host factor tet methylcytosine dioxygenase 2 (TET2) [66]. TET2 protein is well-known for its catalytic activity in the conversion of methylcytosine to 5-hydroxymethylcytosine, and plays important roles in DNA repair, innate immunity, and inflammation [69, 70]. Knockout of TET2 compromises the antiviral effects of IFN α on SADS-CoV replication, which is correlated with the significant downregulation of key ISG including IFITM1 and IFITM3 [66]. TET2 was

previously demonstrated to regulate IFITM3 promoter demethylation to promote IFITM3 expression [71]. However, it remains unknown whether TET2 facilitates type I IFN-mediated inhibition of SADS-CoV replication by regulating IFITM3 expression.

4.2 Evasion of type I IFN-mediated antiviral immunity by SADS-CoV

Viruses have acquired numerous armaments to dampen host antiviral innate immunity during coevolution with their hosts. Thus, it is not surprising that SADS-CoV encodes multiple viral proteins, including N protein,

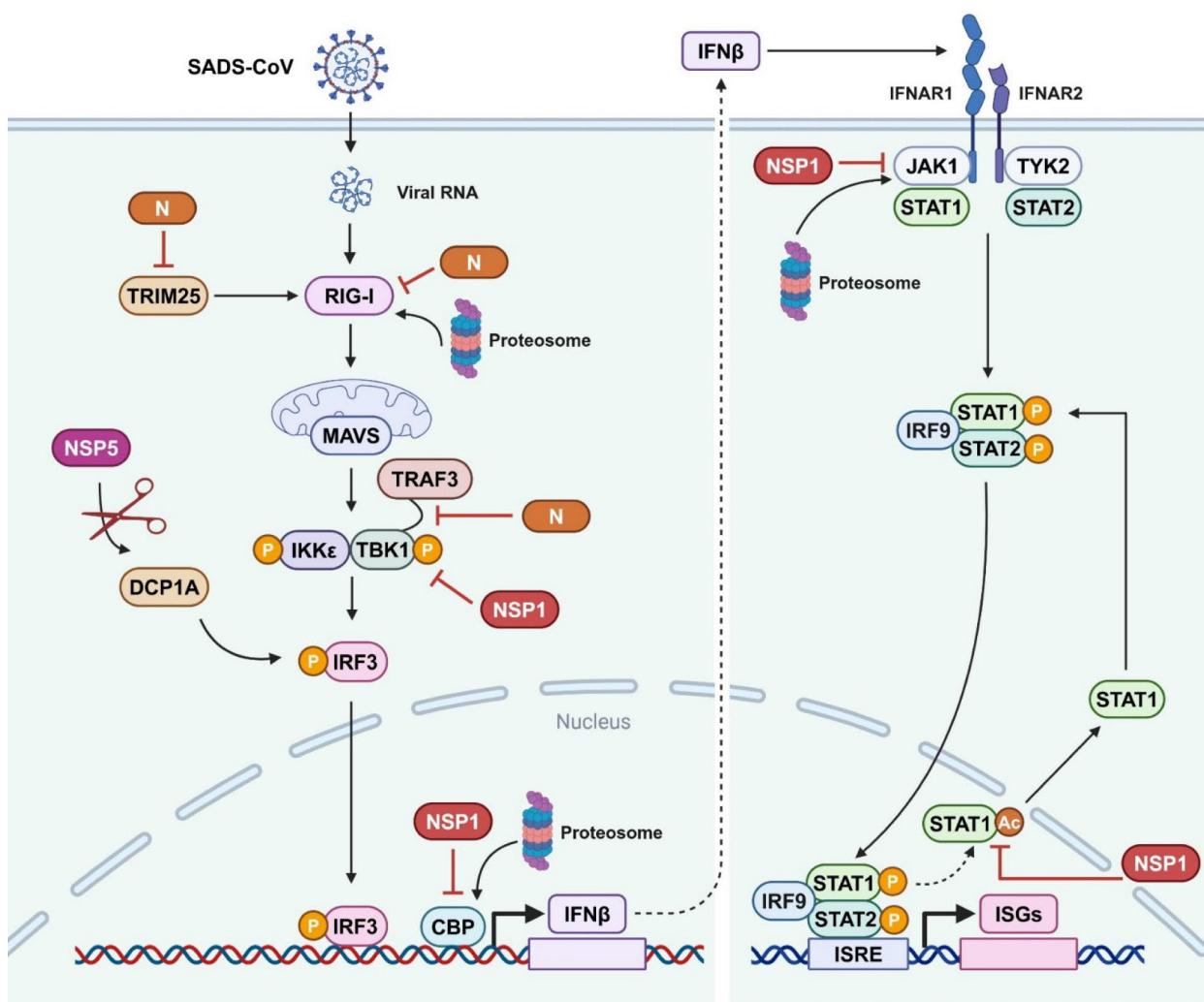


Figure 3 Inhibition of type I IFN response by SADS-CoV. SADS-CoV N protein inhibits IFN β production by (1) inducing RIG-I degradation through ubiquitin proteasome pathway, (2) disrupting TRAF3-TBK1 interaction through interaction with TBK1 and IKK ϵ , (3) interfering with TRIM25 oligomerization and TRIM25-RIG-I interaction through interaction with TRIM25. SADS-CoV NSP1 inhibits IFN β and ISG production by (1) inhibiting TBK1 phosphorylation, (2) inducing CBP degradation through the proteasome-dependent pathway, (3) triggering JAK1 degradation through the ubiquitin proteasome pathway, (4) suppressing STAT1 acetylation and dephosphorylation, blocking its nuclear export. SADS-CoV NSP5 inhibits IFN β production by cleaving DCP1A through its protease activity. Figure created with BioRender.

NSP1, and NSP5, to inhibit type I IFN response in order to evade host antiviral innate immunity and favor its replication (Figure 3).

N proteins of swine enteric coronaviruses, including PEDV and PDCoV, have previously been demonstrated as the potent type I IFN antagonists that inhibit type I IFN production via distinct mechanisms [72, 73]. Consistent with this, SADS-CoV N protein was recently shown to suppress type I IFN production as well [74–76]. Mechanistically, SADS-CoV N protein employs multiple strategies to restrict type I IFN response [74–76]. First, SADS-CoV N protein interacts with RIG-I in an RNA-independent manner and induces its K27-, K48- and K63-linked ubiquitination, which leads to proteasome-dependent degradation of RIG-I and subsequent repression of Sendai virus (SeV)-triggered IFN β production [74]. Second, SADS-CoV N protein interacts with TBK1 and IKK ϵ , which disrupts the interaction between TRAF3 and TBK1, resulting in the reduction of SeV-mediated TBK1 activation and subsequent IFN β production [75]. Lastly, SADS-CoV N protein interacts with the coiled-coil dimerization (CCD) domain of tripartite motif-containing protein 25 (TRIM25), which inhibits TRIM25 oligomerization and interferes with the interaction of TRIM25 and RIG-I, causing the suppression of TRIM25-mediated enhancement of RIG-I signalling and SeV-induced IFN β production [76]. TRIM25 is an important host E3 ubiquitin ligase that regulates antiviral immunity by inducing RIG-I oligomerization through nondegradative K63-linked polyubiquitin to enhance RIG-I signalling [77]. Interestingly, TRIM25 can enhance the antiviral activity of zinc-finger antiviral protein (ZAP) by mediating both K48- and K63-linked polyubiquitination of ZAP [78, 79]. Furthermore, TRIM25 has been demonstrated to interact with influenza virus ribonucleoproteins to inhibit the initiation of RNA chain elongation, thus restricting viral replication [80]. However, the specific mechanism of TRIM25-mediated inhibition of SADS-CoV replication remains unknown.

The NSP1 proteins from swine enteric alphacoronaviruses, including TGEV, PEDV, and SADS-CoV, have a shared function in the inhibition of type I IFN signalling [81]. SADS-CoV NSP1 inhibits TBK1 phosphorylation by disrupting the interaction between TBK1 and the Ub protein, and specifically induces the degradation of CREB-binding protein (CBP) through the proteasome-dependent pathway, thus preventing the formation of IFN transcriptional enhancer and suppressing IFN β production [82]. Intriguingly, SADS-CoV NSP1 induces K11- and K48-linked JAK1 polyubiquitination and triggers JAK1 degradation through the ubiquitin proteasome pathway [83]. Moreover, SADS-CoV NSP1 inhibits STAT1 acetylation and dephosphorylation by inducing

CBP degradation, which blocks STAT1 export from the nucleus to the cytoplasm and restricts ISG expression [83]. These findings reveal two novel mechanisms by which SADS-CoV NSP1 restrains both the RLR signalling pathway and the JAK-STAT signalling pathway to evade type I IFN-mediated antiviral innate immunity.

Coronavirus NSP5, also called 3C-like protease, is not only capable of cleaving viral polypeptides to facilitate viral replication, but also cutting immune-related molecules to evade host antiviral immunity. Specifically, SADS-CoV NSP5 has been demonstrated to target and cleave mRNA-decapping enzyme 1a (DCP1A) to antagonize the type I IFN signaling pathway [84]. DCP1A is well-recognized for its central role in removing the 5'-methyl-guanosine cap from eukaryotic mRNA, and has recently been identified as an antiviral ISG against several viruses [85–87]. SADS-CoV NSP5 cleaves DCP1A via its protease activity, which is dependent on the critical amino acid residues of histidine at 41 and cystine at 144, to inhibit IRF3 and NF- κ B signalling pathways, thus decreasing the expression of IFN β and proinflammatory cytokines [84]. Interestingly, A DCP1A variant with a mutation in glutamine at 343 is resistant to NSP5-mediated cleavage, which displays a stronger inhibitory effect on SADS-CoV replication than wild-type protein [84]. Notably, the NSP5 proteins from different coronaviruses, including SADS-CoV, PDCoV, SARS-CoV, SARS-CoV-2, and MERS-CoV, exhibit similar cleavage activities on DCP1A in infected cells, implicating that NSP5-mediated DCP1A cleavage might be a conserved mechanism by which coronaviruses avoid host antiviral innate immune responses [84, 86].

4.3 Evasion of type III IFN-mediated antiviral Immunity by SADS-CoV

In contrast to the ubiquitous expression of type I IFN receptors, type III IFN receptors are restricted to the mucosal epithelium [88]. Consistent with this, intestinal epithelial cells have recently been shown to express extremely low levels of type I IFN receptors, but produce high levels of type III IFN, thereby triggering robust type III IFN-mediated antiviral immune response against enteric viruses [89]. Therefore, type III IFN-mediated antiviral immunity serves as the primary defence strategy against viruses that replicate in intestinal epithelial cells. Nevertheless, enteric viruses have evolved to employ multiple strategies to evade type III IFN-mediated antiviral immune response. In the case of SADS-CoV, it employs two viral proteins, NSP1 and NS7a, to inhibit the type III IFN response to promote viral replication [65, 67]. SADS-CoV NSP1 prevents poly(I:C)-induced nuclear translocation of IRF1 and induces its degradation through the ubiquitin–proteasome pathway, thus

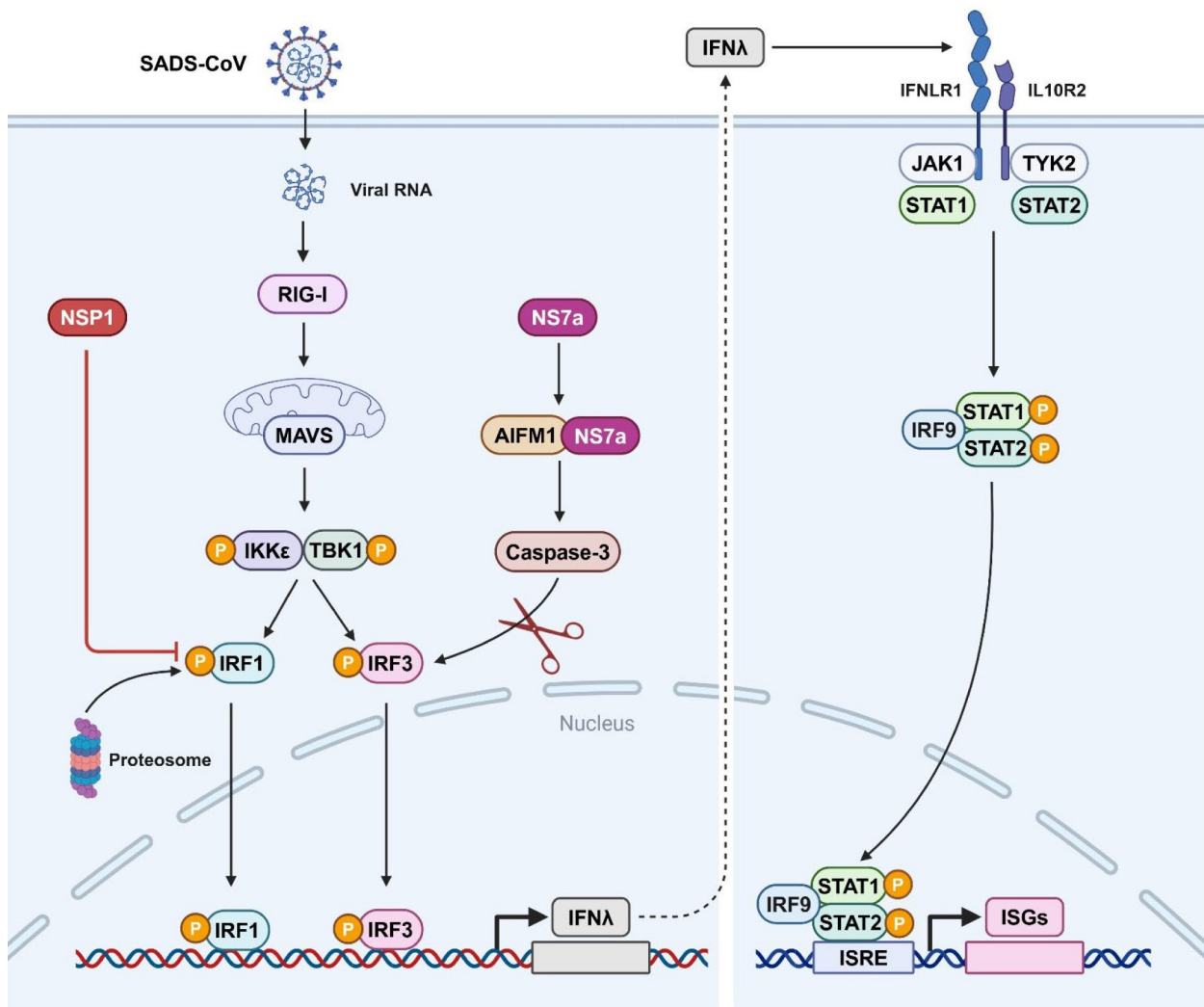


Figure 4 Inhibition of type III IFN response by SADS-CoV. SADS-CoV NSP1 inhibits IFN λ production by inducing IRF1 degradation through the ubiquitin–proteasome pathway. SADS-CoV NS7a inhibits IFN λ production by cleaving IRF3 through activation of caspase-3 by interacting with AIFM1. Figure created with BioRender.

reducing IFN λ expression (Figure 4). However, SADS-CoV NSP1 does not directly interact with IRF1, implicating that it might recruit specific host E3 ubiquitin ligase to degrade IRF1. Additionally, SADS-CoV NS7a interacts with apoptosis-inducing factor mitochondria associated 1 (AIFM1) to activate caspase-3, which cleaves IRF3, thereby inhibiting IFN λ production (Figure 4).

5 SADS-CoV manipulation of autophagy for replication

Autophagy is an evolutionarily conserved catabolic cellular process by which the cellular components including aggregated proteins and damaged organelles are transported to the lysosome for degradation [90,

91]. It is a highly orchestrated cellular process that is tightly regulated by more than 30 autophagy-related genes (ATG) and encompasses four sequential steps: autophagy initiation, elongation and closure of the autophagic membrane, fusion of autophagosome with lysosome, and autophagosome degradation [90, 91]. Under various physiological and pathological conditions including cell development and differentiation, starvation, hypoxia, and virus infection, the highly conserved protein kinase mammalian target of rapamycin (mTOR) is inhibited, and autophagy is thus induced to maintain cellular homeostasis [90, 91]. Inhibition of mTOR signalling allows the formation of the Unc-51 like autophagy activating

kinase 1 (ULK1)-ATG13-FAK family kinase-interacting protein of 200 kDa (FIP200)-ATG101 complex, which phosphorylates and activates the downstream Beclin1-ATG14L-Vacuolar protein sorting 15 (VPS15)-VPS34 complex, leading to the formation of phagophore, an isolated double-membraned vesicle that encapsulates cytosolic components inside itself [92, 93]. The elongation and closure step depends on the ATG16L1-ATG5-ATG12 complex, which facilitates microtubule-associated proteins 1 light chain 3-I (LC3-I) lipidation on the phagophore membrane to form LC3-II, resulting in the formation of autophagosome [92, 93]. Subsequently, the pleckstrin homology domain-containing protein family member 1 (PLEKHM1) tethers autophagosomes by binding to LC3 with lysosomes by interacting with RAB7, and then the fusion between autophagosome and lysosome is triggered by the tail-anchored SNAP receptor (SNARE) syntaxin 17 (STX17), which forms a structure termed autolysosome [92]. Finally, the contents within the autolysosomes are subjected to acidification, and then degraded by lysosomal hydrolases and recycled back to the cytosol [94].

Numerous studies have demonstrated autophagy as a critical branch of the host antiviral innate immunity, which is capable of degrading virions, viral proteins, or even host factors essential for viral replication, and cooperates with host PRR signalling to promote IFN production to inhibit viral replication [92, 95–99]. However, viruses have evolved to employ numerous strategies to evade autophagy or even harness autophagy for their benefits [100–105]. Similar to other swine enteric coronaviruses [106–108], the newly emerged SADS-CoV is also a master that is very good at utilizing autophagy pathway to facilitate viral replication [109, 110]. SADS-CoV infection triggers autophagy not only in Vero E6 cells, swine testis (ST) cells, IPI-2I, and porcine ileum epithelial cells IPI-FX in vitro, but also in the ileal tissues of piglets in vivo [109, 110]. Pharmacological induction of autophagy significantly promotes SADS-CoV replication, while pharmacological inhibition of autophagy or knockdown of autophagy-related proteins compromises SADS-CoV replication, demonstrating a proviral role for autophagy during SADS-CoV infection [109, 110]. Mechanistically, SADS-CoV could utilize two distinct means to induce autophagy to promote viral replication: (1) SADS-CoV infection results in a reduction in the expression of the negative regulator of autophagy, integrin $\alpha 3$ (ITGA3), which inhibits AKT and mTOR phosphorylation, thus inducing autophagy; (2) SADS-CoV infection produces viral membrane-associated PLP2 (PLP2-TM) that interacts with glucose-regulated protein of 78 kDa (GRP78) to form a complex,

which activates ER stress response and the inositol-requiring enzyme 1 (IRE1) signalling pathway, then the JNK-Beclin 1 adaptors bridge the ER stress response and autophagy, demonstrating the critical role for IRE1-JNK-Beclin 1 signalling pathway in SADS-CoV-induced autophagy. However, the specific molecular mechanisms by which (1) SADS-CoV represses ITGA3 expression, (2) ITGA3 inhibits AKT phosphorylation, and (3) SADS-CoV interplays with the autophagy pathway warrant further investigations.

6 SADS-CoV manipulation of apoptosis for replication

Cell death is a normal but critical physiological process in all living organisms by which senescent and damaged cells are removed to maintain cell homeostasis. Of the three most well understood cell death pathways (apoptosis, pyroptosis, and necroptosis), apoptosis was the first to be identified [111, 112]. Apoptosis is a conserved programmed cell death across the animal kingdom, which is induced by various physiological and pathological stimuli and characterized by decreased cell size, membrane blebbing, chromatin condensation, nuclear fragmentation, and the formation of apoptotic bodies [113, 114]. Apoptosis is initiated by two main pathways known as the intrinsic and extrinsic pathways. The intrinsic pathway is triggered by intracellular stressors including growth factors, nutrient deprivation, DNA damage, and ER stress, and is characterized by mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome c into the cytosol, which activates the cascade of caspase-9 signalling to induce cell death [113, 114]. In contrast, the extrinsic pathway is initiated by recognition of extracellular signals by death receptors including Fas receptor (FasR), TNF receptor 1 and 2 (TNFR1/2), and TRAIL receptors DR4 and DR5, which activates the cascade of caspase-8 signalling to induce cell death [113, 114].

Accumulative evidence demonstrates that the PRR of the mammalian innate immune system can activate cell apoptotic pathway [115, 116], suggesting that apoptosis is an essential branch of host innate defence mechanisms against viral infections [117, 118]. However, numerous viruses have evolved to adopt diverse mechanisms to hijack the apoptosis pathway to facilitate viral replication [119–122]. Therefore, it is not surprising that, similar to other swine enteric coronaviruses [106–108, 119], the newly emerged SADS-CoV is also capable of inducing apoptosis to favour viral fitness [67, 123]. SADS-CoV infection induces apoptosis not only in Vero E6, IPI-2I, IPI-FX, and HeLa cells in vitro, but also in the ileal and jejunum tissues of piglets in vivo [67, 123]. SADS-CoV

infection activates the apoptosis initiator caspase-8, which in turn cleaves the proapoptotic BH3-interacting domain death agonist (Bid), cleaved Bid then activates caspase-9, leading to the induction of apoptosis via both the intrinsic and extrinsic pathways [123]. Importantly, both caspase-8 and caspase-9 inhibitors severely block SADS-CoV-induced apoptosis, and thus repress viral replication [123]. Interestingly, activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) signalling pathway is required for SADS-CoV-induced apoptosis, and blocking this pathway significantly inhibits viral replication [124]. Moreover, SADS-CoV NS7a has been demonstrated to activate AIFM1 and caspase-3, which are transported into the nucleus to induce apoptosis, thereby promoting viral replication [67]. Remarkably, the caspase-3 inhibitor Z-DEVD-FMK significantly reduces SADS-CoV replication in the intestinal tissues and elevates the survival rate of infected piglets, demonstrating apoptosis inhibitors as the promising therapeutic drugs for the prevention and control of SADS-CoV infection [67].

7 Conclusions and future perspectives

SADS-CoV is a newly emerged swine enteropathogenic coronavirus that infects a wide range of cells from human and diverse animals, holding potential cross-species transmission risks. The intracellular antiviral immunity is the first line of the host defence system that combats viral infection in an IFN-independent and -dependent fashion. Three host restriction factors, CH25H, TMEM53, and HDAC6, have been demonstrated to target different stages of viral life cycle to restrict SADS-CoV replication (Figure 2). Moreover, both type I and type III IFN are able to potently restrain SADS-CoV replication. However, SADS-CoV has evolved to evade type I- and type III-mediated innate immune responses by encoding multiple viral proteins, including N protein, NSP1, NSP5, and NS7a (Figures 3 and 4). In addition, SADS-CoV has the ability to hijack the autophagy and apoptosis pathways to favour its fitness. Altogether, the interplay between SADS-CoV infection and the host intrinsic and innate immunity is a complex and competitive balance process.

Although much progress has been made to reveal the complicated relationship between SADS-CoV and the host intracellular antiviral immunity in the last few years, it is still not well characterized and needs extensive investigations in the future. As a major topic in future studies, the information on cell-intrinsic immunity is still very limited, which warrants in-depth investigations. To date, there are only three host restriction factors identified to restrain SADS-CoV replication, much more remain to be discovered. While the mutual relationship between SADS-CoV infection and type I and type

III IFN-mediated innate immunity has recently been revealed, the interplay of SADS-CoV and type II IFN-mediated innate immunity remains to be clarified. Furthermore, little is known about the roles of the immune molecules downstream of the IFN signalling pathways, such as ISG, during SADS-CoV replication. Additionally, whether other innate immune responses including DNA damage response, ER stress, stress granules, complement activation, and RNA interference are involved in immune control of SADS-CoV infection is unknown and is thus worthy of future attention. Finally, in-depth and intensive studies on host intrinsic and innate immune factors will undoubtedly promote the identification of new targets for the development of intervention strategies against SADS-CoV infection.

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Author's contributions

FZ, XC, SC, FC, and Yiping Wang conceived and wrote the manuscript, FZ and Yiping Wang made the figures, XH, YZ, QZ, Yiping Wen, RW, SD, and Yiping Wang reviewed and edited the manuscript. All authors read and approved the final manuscript.

Data Availability

Not applicable.

Declarations

Competing interests

The authors declare that they have no competing interests.

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