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Seneca Valley Virus 3C protease negatively regulates the type I interferon pathway by acting as a viral deubiquitinase

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ARTICLE INFO

Keywords:
Deubiquitinase
Innate immunity
Seneca valley virus
Ubiquitin
3C-like protease

ABSTRACT

The mechanisms that enable Seneca Valley Virus (SVV) to escape the host innate immune response are not well known. Previous studies demonstrated that SVV 3C pro suppresses innate immune responses by cleavage of host proteins and degradation of IRF3 and IRF7 protein expression. Here, we showed that SVV 3C protease (3Cpro) has deubiquitinating activity. Overexpressed 3Cpro inhibits the ubiquitination of cellular substrates, acting on both lysine-48- and lysine-63-linked polyubiquitin chains. SVV infection also possessed deubiquitinating activity. The ubiquitin-proteasome system was significantly involved in SVV replication. Furthermore, 3Cpro inhibited the ubiquitination of retinoic acid-inducible gene I (RIG-I), TANK-binding kinase 1 (TBK1), and TNF receptor-associated factor 3 (TRAF3), thereby blocking the expression of interferon (IFN)-β and IFN stimulated gene 54 (ISG54) mRNAs. A detailed analysis revealed that mutations (H48A, C160A, or H48A/C160A) that ablate the Cys and His residues of 3Cpro abrogated its deubiquitinating activity and the ability of 3Cpro to block IFN-β induction. Together, our results demonstrate a novel mechanism developed by SVV 3Cpro to promote viral replication, and may also provide a novel strategy for improving ubiquitination-based therapy.

Seneca Valley Virus (SVV), belonging to the Picornaviridae, is a positive-sense, single-stranded RNA virus that is most closely related to Cardiovirus (Hales et al., 2008). SVV was first isolated in the United States in 2002 as a contaminant in the cell culture of human fetal retinoblasts (Segales et al., 2017). Afterward, a large number of SVV infections, which were characterized by porcine idiopathic vesicular disease, were observed in the United States, Canada, Brazil, and China (Xue et al., 2018). In China, the first case of SVV infection was identified in Guangdong Province in 2015 (Wu et al., 2016). Subsequently, new SVV isolates were identified in Guangdong and Hubei Provinces (Qian et al., 2017; Zhao et al., 2017). In 2017, we also identified a novel SVV strain in Fujian Province in China (Zhu et al., 2017).

Many viruses have evolved strategies to evade innate immune response by inhibiting the host ubiquitination to promote their survival. For instance, human immunodeficiency virus-1 inhibits the antiviral response by the ub-mediated degradation of IRF3 (Okumura et al., 2008), porcine reproductive and respiratory syndrome (PRRS) virus inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation by inhibition of the polyubiquitinating process of IxBα (Sun et al., 2010). To date, SVV 3Cpro has evolved mechanism to cleave or degrade innate immune adaptors to escape the host antiviral innate immune response (Qian et al., 2017; Xue et al., 2018). However, other mechanisms that enable SVV to escape the host innate immune response remain unclear.

To determine whether SVV can evade innate immune response by inhibiting the host ubiquitination, HEK293T cells were transfected with FLAG-tagged VP1, VP2, 2AB, 2B, 2C, 3D, 3C plasmids along with HA-Ub plasmid. At 24 h post-transfection (hpt), the ubiquitinated cellular proteins was assessed by western blotting. The SVV 2A, 2C, and 3C pro inhibited the level of ubiquitinated cellular proteins, and 3C pro most significantly inhibited this process (Supplementary Fig. 1). Human DUBs are classified into five subfamilies based on their catalytic domains structures. They have a high degree of homology in the two regions known as Cys and His boxes that surround the catalytic Cys and His residues (Nijman et al., 2005). Similar to other picornaviruses, SVV 3Cpro also possesses a conserved catalytic box with Cys and His residues (Nijman et al., 2005). To determine whether SVV 3Cpro functions as a DUB, HEK293T cells were transfected with increasing amounts of plasmid encoding 3Cpro along with HA-Ub or empty vector. At 24 hpt, the effect of 3Cpro on all
expression of 3C pro resulted in a dose-dependent reduction of the level of ubiquitinated cellular proteins compared with that in the empty vector-transfected cells. To further determine which Ub linkage type is targeted by 3Cpro, HEK293T cells were transfected with HA-K63-Ub or FLAG-K48-Ub in lieu of HA-Ub. At 24 hpt, the cells were collected for western blotting. Both K48- and K63-linked Ub chains were also processed by 3Cpro in a dose-dependent manner (Fig. 1 B and C).

We also analyzed DUB activity during SVV infection. HEK293T cells were mock infected or infected with SVV at a multiplicities of infection (MOI) of 3 for 12 h. As shown in Fig. 2 A, the levels of endogenous Ub, K48, and K63 ubiquitinated cellular proteins were reduced in SVV-infected cells compared to those in uninfected cells. Taken together, these results confirm that SVV exerts DUB activity during viral infection and 3Cpro is a potent viral DUB that inhibits Ub conjugates formed through K48 or K63 linkages in cellular substrates.

SVV 3Cpro contains Cys and His residues. Therefore, the three mutants, namely the single-site mutants H48A or C160A, and the double-sites mutants H48A/C160A (3Cdm) (Xue et al., 2018), were used to confirm whether the Cys and His residues are involved in the DUB activity of 3Cpro. HEK293T cells were co-transfected with HA-Ub-, HA-K63-Ub-, and FLAG-K48-Ub-expressing plasmids along with FLAG-3C-expressing plasmid or FLAG-3C mutants expressing plasmids. At 24 hpt, the cells were collected for western blotting. All the 3Cpro proteins without Cys and His residues lost the ability to inhibit Ub conjugates compared with the overexpression of wild-type SVV 3Cpro (3Cwt) (Fig. 3 A–C).

To further confirm the DUB activity of SVV 3Cpro, HEK293T cells were transfected with FLAG-3C-expressing plasmid, FLAG-3Cdm expressing plasmid, or empty vector. At 24 hpt, the cells were collected for western blotting. It showed that the 3Cpro proteins without Cys and His residues could no longer reduce levels of endogenous ubiquitinated Ub, K48, and K63 (Fig. 2 B). Taken together, these results indicate that the catalytic Cys and His residues of SVV 3Cpro are required for its DUB activity.

We also investigated whether 3Cpro is associated with the deubiquitination of RIG-I, TBK1, and TRAF3. To do so, HEK293T cells cultured in 10-cm dishes were transfected with various plasmids. At 32 hpt, cell lysates were immunoprecipitated with anti-FLAG or anti-Myc antibody and analyzed by western blotting. Overexpression of 3Cwt significantly inhibited the ubiquitination of RIG-I (Fig. 4A), TBK1 (Fig. 4B), and TRAF3 (Fig. 4C). Overexpression of 3Cdm, which lacks DUB activity, had no such effects. In addition, our results also demonstrated an interaction between 3Cpro and either TBK1, or TRAF3 (Fig. 4B and C). To investigate the interaction between 3Cpro and RIG-I, HEK293T cells were transfected with FLAG-3C-expressing plasmid or empty vector. At 32 hpt, cell lysates were immunoprecipitated with anti-RIG-I antibody and analyzed by western blotting. RIG-I pulled down FLAG-3C (Fig. 4D), which confirmed that 3Cpro interacted with RIG-I.

The interaction of 3Cpro and RIG-I, TBK1, or TRAF3 in context of viral infection was further confirmed. HEK293T cells were mock-infected or infected with SVV (MOI 1) for 12 h. The cell lysates were immunoprecipitated with anti-3C antibody and subjected to immunoblotting analysis. 3Cpro pulled down RIG-I, TBK1, and TRAF3 in SVV-infected cells (Fig. 4E). A reverse immunoprecipitation experiment was subsequently performed using anti-RIG-I, TBK1, or TRAF3 antibody, which showed that RIG-I, TBK1, or TRAF3 also immunoprecipitated 3Cpro (Fig. 4F). These results indicate that the interaction of 3Cpro with RIG-I, TBK1, and TRAF3 in the context of viral infection is involved in the suppression of ubiquitination levels.

Endogenous ubiquitination levels of RIG-I, TBK1, and TRAF3 in SVV-infected cells were further assessed. HEK293T cells were mock infected or infected with SVV (MOI 3) for 12 h. Cell lysates were immunoprecipitated with anti-RIG-I, TBK1, or TRAF3 antibody and analyzed by western blotting. The results showed that the ubiquitination levels of endogenous K48 for TKB1 and K63 for RIG-I and TRAF3 were reduced during SVV infection (Fig. 4G). Taken together, these results indicate that SVV and 3Cpro inhibit the ubiquitination of RIG-I, TBK1, and TRAF3 in a DUB-dependent manner.

Ubiquitination and deubiquitination are important mechanisms that are involved in regulating type I IFN signaling pathways (Peisley et al., 2014). To date, many cellular Ub ligase enzymes can regulate these processes. For example, the E3 ubiquitin ligase RNF128 or Nrdp1 directly enhance ubiquitination of TBK1, which facilitates the activation of TBK1 (Song et al., 2016; Wang et al., 2009). Meanwhile, many cellular DUBs negatively regulate type I IFN signaling pathways. For example, USP3, USP38, and USP19 target RIG-I, TBK1, and TRAF3 for deubiquitination, respectively, thereby blocking the activation of type I IFN signaling pathways (Cui et al., 2014; Gu et al., 2017; Lin et al., 2016). DUB activity also has been demonstrated in many bacteria and viruses, such as Salmonella enterica serovar Typhimurium, FMDV, PRRSV, herpesviruses, coronaviruses, and bunyaviruses, and DUB
Fig. 2. SVV exerts DUB activity during viral infection. (A) HEK-293T cells were seeded in six-well plates, and the monolayer cells were mock infected or infected with SVV (MOI = 3) for 12 h. The levels of endogenousUb-, K63-, and K48-linked cellular proteins were detected by western blotting. (B) HEK-293T cells were seeded in six-well plates, and the monolayer cells were transfected with 1 μg FLAG-3Cwt-expressing plasmid, FLAG-3Cdm-expressing plasmid, or empty vector. At 24 hpt, the levels of endogenous Ub-, K63-, and K48-linked cellular proteins were detected by western blotting.

Fig. 3. SVV 3C<sup>pro</sup> inhibits the ubiquitination of cellular proteins in a manner that is dependent on its DUB activity. (A) HEK-293T cells were seeded in six-well plates, and the monolayer cells were transfected with 1 μg HA-Ub-expressing plasmid along with 1 μg FLAG-3Cwt-expressing plasmid, 1 μg FLAG-3C H48A-expressing plasmid, 1 μg FLAG-3C C160A-expressing plasmid, or 1 μg FLAG-3Cdm-expressing plasmid. The empty FLAG vector was used in the transfection process to ensure that the same number of cells received the same amount of total plasmids. At 24 hpt, the cells were collected for western blotting. Similar transfection and analysis were performed for K63-Ub (B) and K48-Ub (C) as described above.
enzymes play multiple roles in regulating bacterial or viral infections (Fiskin et al., 2016; Sun et al., 2010; van Wijk et al., 2017; Wang et al., 2017). Similar infection and IP experiments were carried out as described above. However, the lysates were immunoprecipitated with anti-RIG-I, TBK1, or TRAF3 antibody and subjected to western blotting. The whole-cell lysates and IP antibody-antigen complexes were analyzed by IB using anti-HA antibody. The input tagged proteins were detected with the indicated antibodies. (D) HEK-293T cells were seeded in 100-mm dishes, and the monolayer cells were transfected with 5 μg FLAG-3C-expressing plasmid or empty vector. At 24 hpt, the cells were lysed and analyzed with a Dual-specific Luciferase reporter assay. HEK293T cells grown in 24-well plates were co-transfected with 0.1 μg/well of the plasmid IFN-β-Luciferase (IFN-β-Luc) along with 0.01 μg/well of plasmid pRL-TK and plasmids encoding FLAG-RIG-I, Myc-TBK1, FLAG-3Cwt, FLAG-3Cdm, or empty vector. At 24 hpt, the cells were lysed and analyzed with a Dual-specific Luciferase Assay kit. As shown in Fig. 5F, RIG-I, and TBK1-mediated IFN-β promoter activity was reduced in the presence of FLAG-3Cwt but not FLAG-3Cdm. To further confirm this effect, we conducted a qPCR analysis to determine the levels of the RIG-I- and TBK1-mediated endogenous transcription of the IFN-β and ISG54 genes. The results showed that FLAG-3Cwt also inhibits RIG-I- and TBK1-induced IFN-β and ISG54 mRNA expression (Fig. 5G), which is in accordance with previous findings showing that SVV 3Cpro significantly reduced the expression of TBK1. SVV 3Cpro possesses protease activity. Therefore, we speculated that 3Cpro reduced the expression of TBK1 by its protease activity, and 3Cpro partly stabilized RIG-I by its DUB activity.

To further investigate whether SVV 3Cpro can block RIG-I- and TBK1-induced type I IFN signaling pathway, we performed a luciferase reporter assay. HEK293T cells grown in 24-well plates were co-transfected with 0.1 μg/well of the plasmid IFN-β-Luciferase (IFN-β-Luc) along with 0.01 μg/well of plasmid pRL-TK and plasmids encoding FLAG-RIG-I, Myc-TBK1, FLAG-3Cwt, FLAG-3Cdm, or empty vector. At 24 hpt, the cells were lysed and analyzed with a Dual-specific Luciferase Assay kit. As shown in Fig. 5F, RIG-I, and TBK1-mediated IFN-β promoter activity was reduced in the presence of FLAG-3Cwt but not FLAG-3Cdm. To further confirm this effect, we conducted a qPCR analysis to determine the levels of the RIG-I- and TBK1-mediated endogenous transcription of the IFN-β and ISG54 genes. The results showed that FLAG-3Cwt also inhibits RIG-I- and TBK1-induced IFN-β and ISG54 mRNA expression (Fig. 5G), which is in accordance with previous findings showing that SVV 3Cpro significantly reduced the expression of TBK1. SVV 3Cpro possesses protease activity. Therefore, we speculated that 3Cpro reduced the expression of TBK1 by its protease activity, and 3Cpro partly stabilized RIG-I by its DUB activity.

In the present study, we provide direct evidence that SVV 3Cpro is a novel viral deubiquitinating enzyme. However, more work will be required to determine if other picornavirus 3Cpro, such as echovirus 71, coxsackievirus A16, or FMDV, have DUB activity. Our data also uncover a novel mechanism by which SVV 3Cpro antagonizes type I IFN induction, i.e., deubiquitinating the critical signaling molecules RIG-I, TBK1, and TRAF3. Our results comparing various 3Cpro mutants suggest that the DUB activity of 3Cpro enables it to block induction of the IFN-β promoter and the

| Table 1 | The qPCR primers used in this study. |
|--------|---------------------------------|
| Primers | Sequences (5’-3’) | Target gene |
| hIFN-β-F | GACATCCCTGAGGAATAG | human IFN-β gene |
| hIFN-β-R | AGATTTGGAACATCCAG | |
| hISG54-F | ACGGTAAGTGGACAGGTTG | human ISG54 gene |
| hISG54-R | AGGTGAGTTCCCAAGTG | |
| hISG56-F | AATGACAGCAGGATAAGG | human ISG56 gene |
| hISG56-R | GAAGAATGTTCAATGCT | |
| SVV-F | AGAATTGGAACAGCAGCT | SVV gene |
| SVV-R | GAGCAAGCTAGACAGATG | |
| IPAD1-F | GGGCAACGTTGTAGCAATGG | human GAPDH gene |
| IPAD1-R | GCCAGTATGGCATGGACTG | |

The ubiquitin-proteasome system (UPS) plays important roles in the degradation of proteins, the immune response, and signal transduction (Casorla-Perez et al., 2017). The UPS is a double-edged sword in viral pathogenesis: the UPS is necessary for many viruses replication by maintaining the proper functions of viral proteins (Barrado-Gil et al., 2017; Luo, 2016; Wang et al., 2016); the UPS can constitute host immune system to reduce viral replication (Luo, 2016). For example, the UPS was essential for coronavirus replication (Raaben et al., 2010), whereas coronavirus papain-like proteases can act as DUBs that block type 1 IFN production (Clementz et al., 2010). Proteasome inhibitors MG132 can inhibit the UPS. To determine the impact of the UPS on the replication of SVV, HEK293T cells were infected with an equal amount of SVV (MOI 1). At 4 hpi, the cells were incubated with or without MG132 for 8 h. Viral RNA and protein levels were examined. MG132 significantly inhibited replication of SVV (Fig. 5C), which indicated that the UPS was also essential for SVV replication. Therefore, we speculated that the UPS plays an important role in maintaining functions of SVV proteins.

The abundance of RIG-I, TBK1, and TRAF3 during SVV infection remained unclear. HEK293T cells cultured in 6-well plates were mock infected or infected with SVV. The abundance of RIG-I, TBK1, and TRAF3 were compared at 0, 6, and 12 h after SVV infection. The results showed that SVV infection had no impact on the abundance of RIG-I and TRAF3, but did inhibit expression of TBK1 (Fig. 5D). It is well known that reduction of the K48-linked polyubiquitin can stabilize TBK1. However, our results indicated that SVV or 3Cpro reduced expression of TBK1. To clarify this unexpected result, a broad-range deubiquitinase inhibitor, PR-619 (Sigma-Aldrich), was selected for further study (Altun et al., 2011). The ubiquitination levels of endogenous K48 for TBK1 was enhanced after PR-619 incubation (Supplementary Fig. 2). HEK293T cells were transfected with FLAG–3C-expressing plasmid or infected with SVV (MOI 1). Then, the cells were treated with or without PR-619. Cell lysates were analyzed by western blotting. The expression of TBK1 in the 3Cpro-transfected and SVV-infected cells was enhanced comparing with that in the PR-619-treated cells (Fig. 5E), which indicated that 3C-induced reduction of the K48-linked polyubiquitin of TBK1 enhanced the expression of TBK1. However, as a whole, 3Cpro and SVV still reduced the expression of TBK1. SVV 3Cpro possesses protease activity. Therefore, we speculated that 3Cpro reduced the expression of TBK1 by its protease activity, and 3Cpro partly stabilized TBK1 by its DUB activity.
endogenous transcription of the IFN-β and ISG54 genes. Studies have indicated that SVV Cpro mutants that abrogate Cys and His residues lost protease activity (Qian et al., 2017; Xue et al., 2018). Here, our results indicated that SVV Cpro mutants that abrogate Cys and His residues also lost DUB activity. Therefore, we speculate that the Cys and His residues of SVV Cpro may contribute to both protease and DUB activities. Cpro might suppress type I IFN response by different mechanisms in host cells.

SVV has been identified as a novel oncolytic virus against several human cancers (Burke, 2016). Ubiquitination and deubiquitination are mechanisms that also play important roles in regulation of cancer (Kaushal et al., 2018). Whether SVV can inhibit cancer progression through Cpro DUB activity is still unclear and will need to be investigated in future studies. It may provide a novel method for cancer therapy.
Fig. 5. SVV 3Cpro inhibits RIG-I- and TBK1-induced type I IFN production. (A) HEK293T cells were seeded in 12-well plates, and the monolayer cells were co-transfected with 0.5 μg FLAG-3Cwt-expressing plasmid, FLAG-3Cdcm-expressing plasmid, or empty vector. At 24 hpt, the cells were mock infected or infected with SVV (100 hemagglutinating activity units) for 12 h. The expression of IFN-β, ISG54, and ISG56 mRNAs was determined with qPCR assay. (B) HEK293T cells were seeded in 6-well plates, and the monolayer cells were transfected with 1 μg FLAG-3C-expressing plasmid or empty vector. At 24 hpt, the cells were infected with an equal amount of SVV (MOI 1) for 12 h. Expression of viral RNA was determined by qPCR assay. Expression of viral VP1 protein was detected by western blotting. (C) HEK293T cells were seeded in 6-well plates, and the monolayer cells were transfected with 1 μg FLAG-3C-expressing plasmid or infected with SVV (MOI 1). At 4 hpi, the cells were incubated with or without 20 μM MG132 for 8 h. Expression of viral RNA was determined by qPCR assay. Expression of viral VP1 protein was detected by western blotting. (D) HEK293T cells were seeded in 6-well plates, and the monolayer cells were mock infected or infected with SVV (MOI 1) for 0, 6 and 12 h. Expression of TBK1, RIG-I, TRAF3, and viral VP1 proteins were detected by western blotting. (E) HEK293T cells were seeded in 6-well plates, and the monolayer cells were transfected with 1 μg FLAG-3Cdcm-expressing plasmid or infected with SVV (MOI 1). Then, the cells were treated with or without 25 μM PR-629 for 6 h. Cell lysates were analyzed by western blotting. (F) HEK293T cells grown in 24-well plates were co-transfected with 0.1 μg/well of IFN-β-Luc along with 0.01 μg/well of pRL-TK plasmid and 0.1 μg/well of plasmids encoding FLAG-RIG-I, Myc-TBK1, FLAG-3Cwt, FLAG-3Cdcm, or empty vector. At 24 hpt, the cells were lysed. The Dual-specific Luciferase Assay kit was used to analyze the luciferase activities of firefly and Renilla. The data represent the means and standard deviations from three independent experiments. (G) HEK-293T cells were seeded in six-well plates, and the monolayer cells were co-transfected with 1 μg FLAG-RIG-I-expressing plasmid, 1 μg FLAG-3Cdcm-expressing plasmid, 1 μg FLAG-3C-expressing plasmid, or 1 μg empty vector. The empty vector was used in the transfection process to ensure that the same number of cells received the same amount of total plasmids. Similar transfection were performed for Myc-TBK1 as described above. At 24 hpt, the expression of IFN-β and ISG54 mRNAs was determined with qPCR assay.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgments

This work was supported by grants from the National Natural Sciences Foundation of China (no. U1501213 and 31672585), the National Key Research and Development Program of China (2016YFD0500901), the Gansu Science Foundation for Distinguished Young Scholars (no. 1606RJYA280) and the Gansu Science Foundation for Young Scholars (1606RJYA280).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2018.10.028.

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