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BRIEF REPORT

Antiviral activity of canine interferon lambda 3 expressed using a recombinant adenovirus against canine coronavirus, canine parvovirus, and canine distemper virus

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Abstract

Canine coronavirus (CCoV), canine parvovirus (CPV), and canine distemper virus (CDV) are highly contagious canine pathogens; dogs with these diseases are difficult to treat. In a previous study, we developed a recombinant adenovirus expressing canine interferon lambda 3 (Ad-caIFNλ3) in canine epithelial cells. In this study, we aimed to investigate the antiviral activity of Ad-caIFNλ3 against CCoV, CPV, and CDV in two canine cell lines, A72 and MDCK. Ad-caIFNλ3 transduction suppressed replication of these viruses without cytotoxicity. Our results suggest that Ad-caIFNλ3 may be a therapeutic candidate for canine viral diseases.

Keywords Canine coronavirus (CCoV) · Canine parvovirus (CPV) · Canine distemper virus (CDV) · Recombinant adenovirus · Canine interferon lambda 3 · Therapeutics · In vitro

Introduction

Canine coronavirus (CCoV) and canine parvovirus (CPV) are highly contagious viral pathogens that commonly cause acute gastroenteritis in dogs (Mia et al. 2021; Hamid et al. 2022). Canine distemper virus (CDV) causes systemic disease by affecting gastrointestinal, respiratory, and central nervous systems. Moreover, it induces a severe long-lasting immunosuppression (Beineke et al. 2009; Mia et al. 2021). Vaccines help control the spread of these canine infectious diseases and reduce their severity by alleviating clinical signs (Larson and Schultz 2021). In spite of current systems for vaccination, dogs are still hospitalized as a result of infectious diarrhea caused by CCoV, CPV, and CDV. Moreover, these diseases are considered a challenge to treat (Gizzi et al. 2014; Tizard 2021).

Interferons (IFNs), a group of cytokines that induce antiviral response, are classified into three types (types I, II, and III) (De Andrea et al. 2002; Negishi et al. 2018). Type I and III IFNs induce JAK/STAT signaling pathway, achieving an antiviral state through the expression of interferon stimulated genes (ISGs) (De Andrea et al. 2002; Pervolaraki et al. 2018). The distribution of type I IFN receptors is ubiquitous due to systemic expression on cell surfaces in the body; however, type III IFN receptors are preferentially expressed in epithelial cells, suggesting functional differences (Pervolaraki et al. 2018). The restricted distribution of type III IFN receptors may reduce the side effects of excessive inflammatory responses (Lazear et al. 2019).

Antiviral treatment using IFNs has mainly been used as a recombinant protein expressed in *Escherichia coli*; the recombinant protein, which is hampered by its short half-life, has to be injected in a large dose daily (Julander et al. 2007). An adenovirus vector-mediated IFN expression system to improve the half-life of IFN is an alternative strategy that can effectively deliver and elicit expression of IFN (Demers et al. 2002; Wu et al. 2007; Kim et al. 2014).

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Methods and results

In a previous study, we developed a recombinant adenovirus expressing canine interferon lambda 3 (Ad-caIFNλ3), and its expression could be regulated by the presence of doxycycline (Kim et al. 2021b). Cells transduced with Ad-caIFNλ3 in the presence of doxycycline prevented canine interferon lambda 3 (IFNλ3) production, leading to a 10-fold increase in number of recombinant adenoviruses produced. The infectious unit (IFU) of Ad-caIFNλ3 was calculated using an immunocytochemistry assay kit (Adeno-X™ Rapid Titer Kit, Takara Bio), which could detect hexon proteins of the recombinant adenoviruses. Evaluation of the results were conducted according to the manufacturer's instructions as follows: (infected cells/field) × (fields/well) / (volume virus (mL) × (dilution factor). As a result, 8.82×10^7 IFU/mL in 100X magnification and 5.00×10^7 IFU/mL in 200X magnification were calculated without doxycycline treatment group. When the doxycycline was treated, 5.67×10^8 IFU/mL in 100X magnification and 6.00×10^8 IFU/mL in 200X magnification was calculated showing that treatment of doxycycline could induce higher production of recombinant adenoviruses (Fig. 1A). Transmission electron microscopy also confirmed that approximately 100 nm of recombinant adenovirus was assembled at P3 (Fig. 1B).

To verify that Ad-caIFNλ3 would not be toxic to the canine cells used in this study, A72 and MDCK cell lines derived from dog tissue were treated with Ad-caIFNλ3 up to 200 multiplicities of infection (MOI) (Supplementary Fig. 1A). To compare changes in cell viability, we performed 2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, as described previously (Kim et al. 2021b). Quantitative changes in viable cell amounts transduced by a specific MOI of Ad-caIFNλ3 were compared between groups that did not receive Ad-caIFNλ3. In both cell lines, Ad-caIFNλ3 transduction-induced cell toxicity was not observed up to 200 MOI. An enzyme-linked immunosorbent assay (ELISA) was conducted, as described previously (Kim et al. 2021b), to determine whether canine IFNλ3 was produced by Ad-caIFNλ3 transduction in canine-derived cell lines (Supplementary Fig. 1B). Three days after transduction, the cell supernatants were harvested and centrifuged at 1200 × g to eliminate cell debris. In the A72 cell line, the supernatant of MOCK cells contained 434.400 ± 89.109 pg/mL of canine IFNλ3. When Ad-caIFNλ3 transduction was conducted at 10 and 100 MOI, the concentration of canine IFNλ3 increased to 6235.407 ± 1078.882 pg/mL and 9503.857 ± 848.919 pg/mL, respectively. In the MDCK cell line, the supernatant of MOCK cells contained 467.023 ± 156.522 pg/mL of canine IFNλ3. When Ad-caIFNλ3 transduction was conducted at 10 and 100 MOI, the concentration of canine IFNλ3 increased to 6526.297 ± 1209.603 pg/mL and 9429.537 ± 654.385 pg/mL, respectively. In both cell lines, Ad-caIFNλ3 induced canine IFNλ3 expression in a dose-dependent manner.

CCoV (ATCC No. VR-2068), CPV (KVCC No. VR-1500039), and CDV (KVCC-VR1900056), which are infectious viral pathogens in dogs, were used to confirm the antiviral efficacy of Ad-caIFNλ3 in cell culture systems. A72 cell line was used for propagation of CCoV and CPV, while MDCK cell line was used for CDV infection. These cell lines were infected with the respective viruses at an MOI of 0.001, and Ad-caIFNλ3 transduction (10 MOI and 100 MOI) was conducted one day pre-infection (− 1 dpi), on the same day as infection (0 dpi), and one day post-infection (1 dpi). Total DNA or RNA was extracted using the Patho Gene-spin DNA/RNA Extraction Kit (iNtRON Biotech) at 3 dpi according to the manufacturer's instructions. Then, changes in viral DNA or RNA were compared using

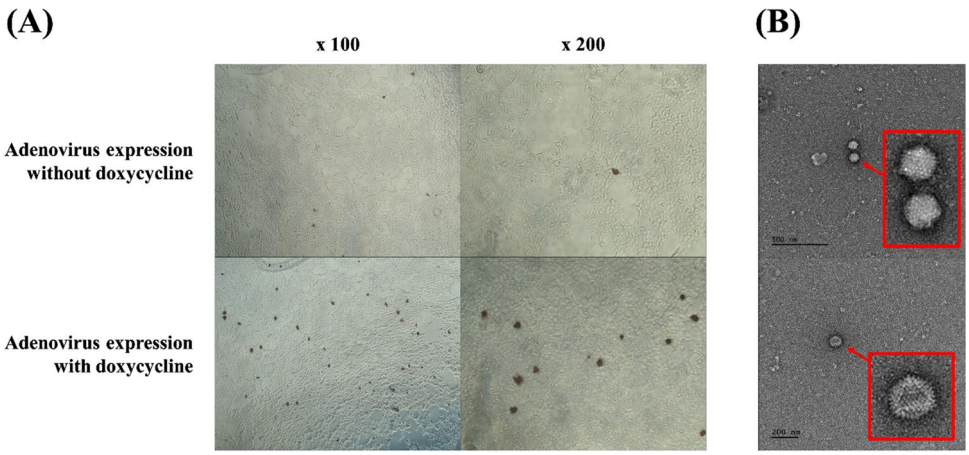

Fig. 1 Identification of recombinant adenovirus formation. (**A**) Hexon proteins of recombinant adenovirus were detected using immunocytochemistry (ICC) assay at three days after transduction. Representative figures are microscopic field of ICC results infected with diluted virus ($\times 10^{-5}$). More recombinant adenovirus particles were produced with 10 µg/mL doxycycline treatment than when doxycycline was not used. (**B**) Recombinant adenovirus particles were identified using transmission electron microscope (TEM)

quantitative polymerase chain reaction (qPCR). The following primers were used: 1) CCoV: forward primer, 5′-TTG ATC GTT TTT ATA ACG GTT CTA CAA-3′; reverse primer, 5′-AAT GGG CCA TAA TAG CCA CAT AAT-3′; 2) CPV: forward primer, 5′-GAC GAC AGC ACA GGA AAC AA-3′; reverse primer, 5′-GTT GTG CCA TCA TTT CA-3′; 3) CDV: forward primer, 5′- AGC TAG TTT CAT CTT AAC TAT CAA ATT-3′; reverse primer, 5′-TTA ACT CTC CAG AAA ACT CAT GC-3′; and 4) canine GAPDH: forward primer, 5′-GGT CAC CAG GGC TGC TTT-3′; reverse primer, 5′-ATT TGA TGT TGG CGG GAT-3′. qPCR was performed using the One Step TB Green® PrimeScript™ RT-PCR Kit (Takara Bio) for RNA and PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific) with a Light Cycler instrument (Roche Diagnostics). Fold change of viral DNA or RNA in the supernatant was compared with the positive control group that were infected only by CCoV, CPV, or CDV without Ad-caIFNλ3 transduction. For cell lysate, viral RNA or DNA levels relative to GAPDH, a housekeeping gene, were calculated using delta-delta CT method and compared with the positive control group. As the MOCK control group, recombinant adenovirus containing the GFP gene was used. CCoV RNA replication was significantly suppressed when 10 MOI of Ad-caIFNλ3 was transduced − 1 dpi ($p < 0.001$) and 0 dpi ($p < 0.01$) in the supernatant and − 1 dpi ($p < 0.01$) in the cell lysate. At 100 MOI of Ad-caIFNλ3, CCoV RNA replication was suppressed in all the experimental groups (Fig. 2A and Supplementary Fig. 2A). CPV DNA replication was significantly suppressed when 10 MOI of Ad-caIFNλ3 was transduced − 1 dpi ($p < 0.001$) in the supernatant, and − 1 dpi ($p < 0.001$) and 0 dpi ($p < 0.01$) in the cell lysates. At 100 MOI of Ad-caIFNλ3, CPV DNA replication was significantly suppressed ($p < 0.001$) in all experimental groups (Fig. 2B and Supplementary Fig. 2B). CDV RNA replication was significantly suppressed when 10 MOI of Ad-caIFNλ3 was transduced − 1 dpi ($p < 0.01$) in the supernatant, and − 1 dpi ($p < 0.001$) and 0 dpi ($p < 0.05$) in the cell lysates. At 100 MOI of Ad-caIFNλ3, CDV RNA replication was suppressed at − 1 dpi ($p < 0.05$) in the supernatant and − 1 dpi ($p < 0.001$), 0 dpi ($p < 0.01$), and 1 dpi ($p < 0.05$) in the cell lysates (Fig. 2C and Supplementary Fig. 2C). To measure the reduction in the infectious viral particle, plaque assay was conducted. Cell lysates and supernatants from the positive control and experimental groups (100 MOI and -1 dpi transduction) at 3 dpi were harvested and used for plaque assay as described previously (Kim et al. 2021b). The results showed that plaque

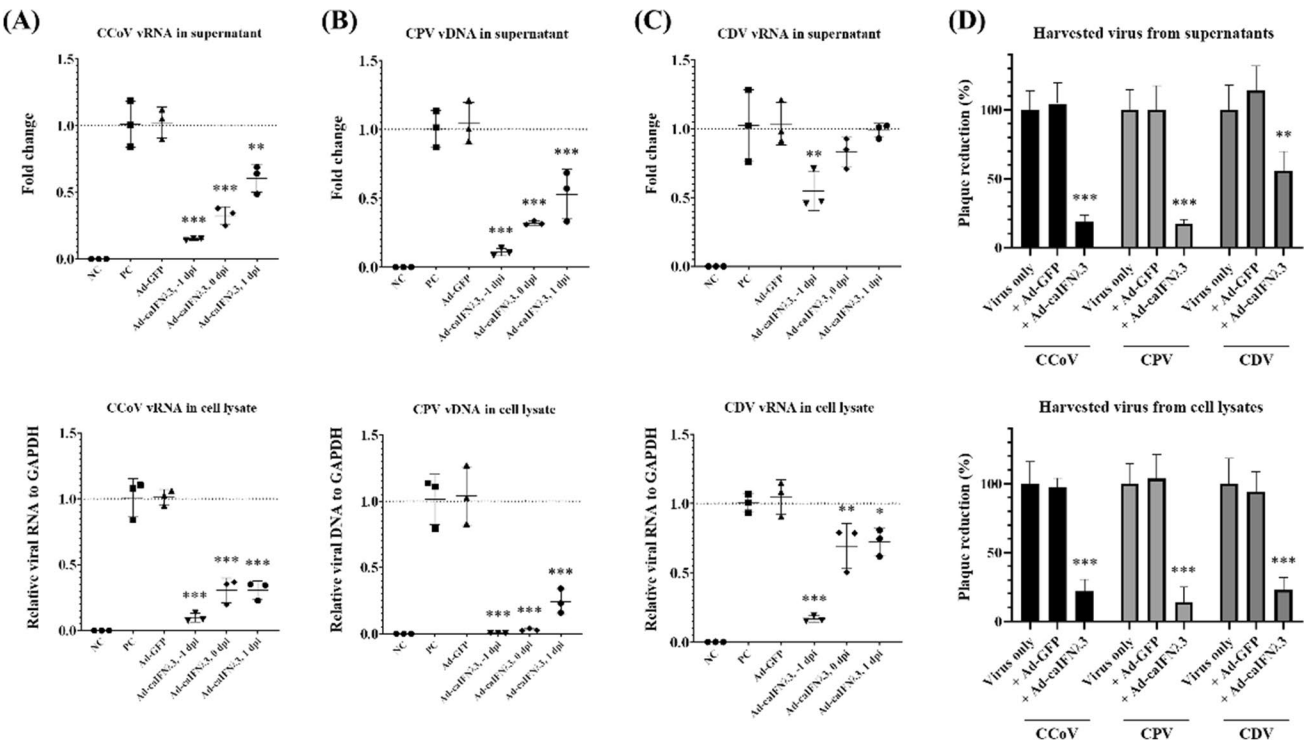

Fig. 2 Antiviral activity of Ad-caIFNλ3 (100 MOI) against CCoV, CPV, and CDV. Quantitative polymerase chain reaction (qPCR) was conducted to compare the amount of replicated viral genes. Cells were infected with each virus and transduced with Ad-caIFNλ3 (100 MOI). Ad-GFP (100 MOI) was used as the MOCK control group. Viral DNA or RNA levels of (**A**) CCoV, (**B**) CPV, or (**C**) CDV were analyzed from cell culture medium and cell lysate at three days post-infection. (**D**) Ad-caIFNλ3 transduction at -1 dpi reduced plaque production by rescued viruses. Data are presented as mean ± SD of at least three independent experiments. NC: negative control, PC: positive control. Data are presented as mean ± standard deviations (SD) of three independent experiments. Statistical analysis was conducted using 2-way ANOVA with dunnett's multiple comparisons test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

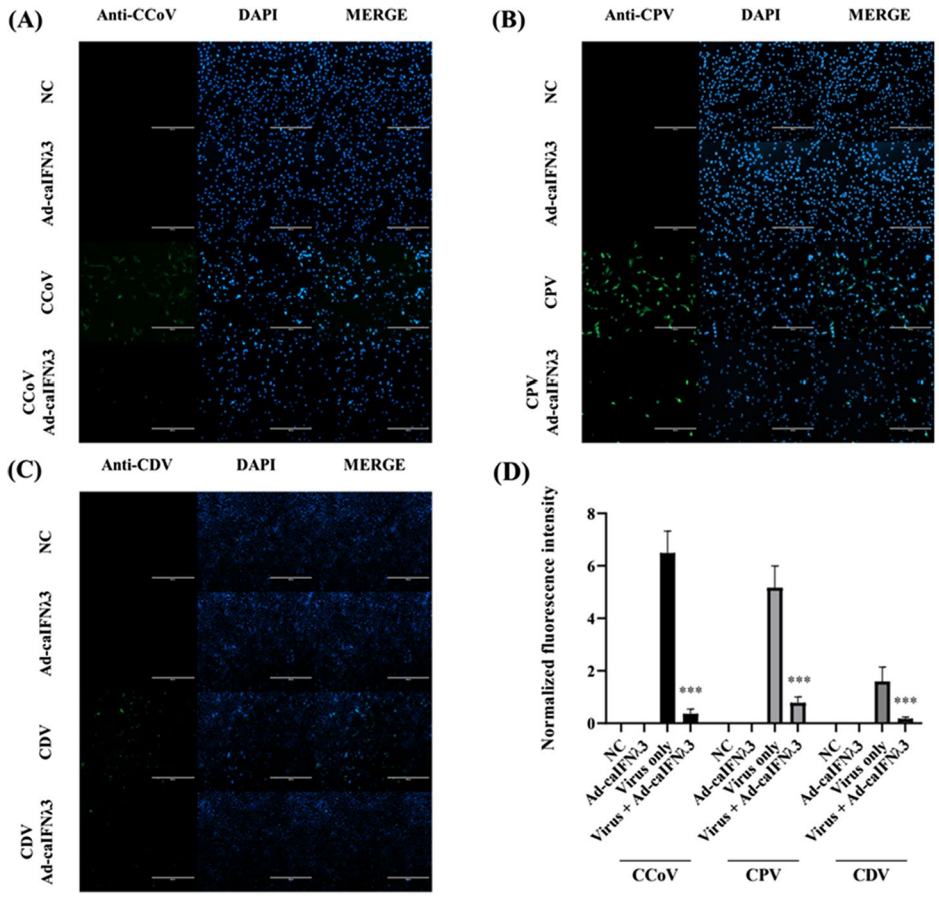

Fig. 3 Comparison of the viral protein expression using immunofluorescence assay. Immunofluorescence assay (IFA) was conducted 1 day after (**A**) CCoV, (**B**) CPV, or **(C)** CDV infection. One day after Ad-caIFNλ3 transduction, A72 cell line was infected with CCoV or CPV, and MDCK cell line was infected with CDV. Viral infection was confirmed through green fluorescence. DAPI was used for nuclear counter staining. (**D**) Quantitative data of fluorescence intensity were calculated using ImageJ software. Data are presented as mean ± standard deviations (SD) of three independent experiments. Statistical analysis was conducted using 2-way ANOVA with dunnett's multiple comparisons test. NC: negative control. $*p < 0.05$

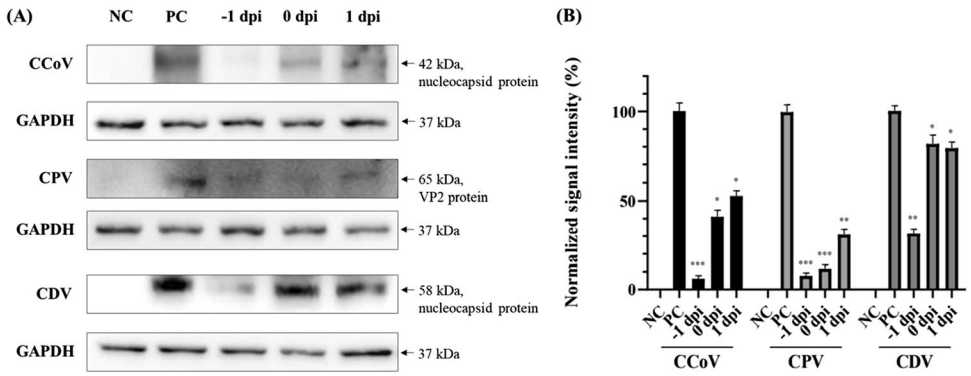

Fig. 4 Suppression of viral protein expression by Ad-caIFNλ3 transduction. (**A**) Western blot assay was conducted 3 days after canine virus infection. Infected cells were transduced by Ad-caIFNλ3 at − 1 dpi, 0 dpi, or 1 dpi. GAPDH, housekeeping protein, showed that the same number of cells were used in these experiments. (**B**) Quantitative data of signal intensity were calculated using ImageJ software. Data are presented as mean ± standard deviations (SD) of three independent experiments. Statistical analysis was conducted using 2-way ANOVA with dunnett's multiple comparisons test. NC: negative control, PC: positive control. $*p < 0.05$, $***p < 0.001$

production by rescued viruses decreased when Ad-caIFNλ3 transduction was conducted than when only CCoV, CPV, or CDV were infecting the cell lines.

The suppression of viral protein expression was compared using immunofluorescence assay (IFA) and western blot assay. For IFA, A72 and MDCK cells were transduced with Ad-caIFNλ3. One day after canine virus infection, we performed IFA, as described previously (Kim et al. 2021a). CCoV, CPV, and CDV were bound to mouse anti-canine coronavirus nucleoprotein antibody (M938, Biozol Diagnostica), mouse anti-canine parvovirus monoclonal antibody (HM860, EastCoast Bio), and mouse anti-canine distemper virus monoclonal antibody (LS-C77663, LSBio), respectively. Primary antibodies bound to each virus were detected using goat anti-mouse IgG (H + L) secondary antibody Alexa Fluor™ Plus 488 (A32723, Thermo Fisher Scientific) when green fluorescence was emitted. Green fluorescence was not detected in either the negative control (NC) group or the Ad-caIFNλ3 transduction group without viral infection in any of the experiments. When infected with CCoV (Fig. 3A), CPV (Fig. 3B), or CDV (Fig. 3C), green fluorescence was detected in the cytoplasm and nucleus of the host cells, and the amount of fluorescence decreased in the group transduced with Ad-caIFNλ3 at one day pre-infection.

For the western blot assay, cell lysates were collected, and the expression levels of viral proteins were analyzed at 3 dpi (Fig. 4A). Briefly, cell lysis was performed using 2×Laemmli sample buffer (S3401, Sigma), and supernatants of the cell lysates were used for viral protein detection. The proteins were subjected to sodium dodecyl sulfate–polyacrylamide gel electrophoresis and then transferred to a nitrocellulose membrane and blocked with 5% skim milk in phosphate buffered saline with 0.05% tween 20, pH 7.4 (PBS-T) overnight at 4 °C. The primary antibodies used in IFA were captured with secondary antibodies tagged with horseradish peroxidase and visualized using the SuperSignal™ West Pico PLUS Chemiluminescent Substrate (Sigma). The results confirmed that the expression of viral proteins decreased when Ad-caIFN λ3 was transduced than when only CCoV, CPV, or CDV were infecting the cell lines. The fluorescence and signals of immunofluorescence and western blot assays were analyzed using ImageJ software.

Discussion

Canine viral gastroenteritis remains an ongoing problem in animal hospitals and shelters despite the availability of vaccines (Gizzi et al. 2014; Pesavento and Murphy 2014; Radford et al. 2021). Generally, treatment for canine gastroenteritis is conducted with fluid maintenance in animal hospitals (Kumar 2020). Antiviral drugs such as type I IFNs, including IFN α, IFN β, and IFN ω, have been used to reduce viral load (Scott-Morris and Walker 2015; Klotz et al. 2017). However, multiple side effects, including nausea, diarrhea, hemolytic anemia, or fever, have been reported for type I IFN usage (Borden 2019; Mueller and Hartmann 2021). To overcome these disadvantages, IFN λ—a type III IFN—has recently been suggested as an alternative antiviral drug (Andreakos and Tsiodras 2020).

The expression of cloned IFNs in the adenoviral vector could interfere with the production of recombinant adenoviral vector itself (Murphy et al. 2005). To prevent this problem, the tetracycline operator system described in our previous study was applied, and a higher yield of recombinant adenoviruses was obtained (Kim et al. 2021b).

Ad-caIFNλ3 transduction developed in our study induced canine IFNλ3 expression, which activated antiviral response by expressing IFN stimulated genes (Mx1, OAS1, and ISG15) and subsequently suppressed the replication of canine influenza virus in canine cell lines (Kim et al. 2021b). In a series of studies, we further verified the suppression of CCoV, CPV, and CDV replication when canine IFNλ3 was expressed using Ad-caIFNλ3 in virus-infected cells. In time-of-addition experiments, A72 and MDCK cell lines were transduced with a specific MOI of Ad-caIFNλ3 -1 dpi, 0 dpi, and 1 dpi. For all viruses, the earlier the cells were transduced by Ad-caIFNλ3, the greater the suppression of both viral genome and protein levels. This could be the result of earlier expression of canine IFNλ3 by the recombinant adenovirus (Du et al. 2019). In a similar context, inhibitory effects were better in a dose-dependent manner, showing better prevention in the cells treated with an MOI of 100 than those treated with an MOI of 10.

In this study, we confirmed that Ad-caIFNλ3 transduction into target cells could suppress the replication of infectious viruses such as CCoV, CPV, and CDV in an *in vitro* system. Our findings will contribute significantly to the development of therapeutic drugs for these viral diseases in dogs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11259-022-10000-1.

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Authors' contributions D.-H.K. and I.-S.C. conceived, designed, and validated the study. S.-H.H., H.-J.G., D.-Y.K., and J.-H.K. prepared and conducted the experiments. J.-B.L., S.-Y.P., C.-S.S., S.-W.L., and I.-S.C. supervised experiments. D.-H.K. and I.-S.C. wrote the main manuscript and prepared all the figures. I.-S.C. contributed to the funding acquisition. All authors have reviewed the final manuscript and approved its submission.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Not applicable.

Consent to publish Not applicable.

Competing interests The authors declare that they have no competing interests.

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