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Short communication

Basal interferon signaling and therapeutic use of interferons in controlling peste des petits ruminants virus infection

Qiuyan Chang[a,1], Fucheng Guo[a,1], Junlin Liu[a], Derong Zhang[a], Yuping Feng[a], Xiao-xia Ma[a,b,*], Youjun Shang[b,**]

[a] Center for Biomedical Research, Northwest Minzu University, Gansu 730030, PR China
[b] State Key Laboratory of Veterinary Etiological Biology, Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou, Gansu, PR China

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ABSTRACT

Peste des petits ruminants virus (PPRV) is a morbillivirus which causes severe disease in ruminants. Since interferons (IFNs) serve as the important defense line against viral infection, we have investigated the roles of types I and III IFNs in PPRV infection *in vitro*. Upon PPRV infection, IFN-λ3 was strongly induced, while IFN-β and IFN-λ2 were moderately induced at transcriptional level in human embryonic kidney 293 T (HEK293T) cells. Although the transcription of type I and III IFNs were triggered, the production of functional IFN products was not detected. Importantly, the replication of PPRV was strongly inhibited in HEK293T cells treated by the exogenous IFNs (IFN-α-2b, IFN-β and IFN-λ3). Consistently, these IFNs significantly activate a panel of IFN-stimulated genes (ISGs). The inhibition of JAK-STAT pathway by JAK I inhibitor can abrogate the anti-PPRV activity of IFNs. Thus, our study shall contribute to better understanding of the complex PPRV-host interactions and provide rationale for therapeutic development of IFN-based treatment against PPRV infection.

1. Introduction

Peste des petits ruminants (PPR) is caused by a *Morbillivirus* which is classified into the family *Paramyxoviridae*. PPR is an acute, highly contagious and fatal disease primarily threatening small ruminants (Kumar et al., 2014). PPR can cause severe economic losses, and this disease is featured by conjunctivitis, rhinitis, stomatitis, pneumonia and enteritis, and also immunosuppression (Baron et al., 2016). PPRV is an enveloped, single-stranded, non-segmented, negative RNA virus. Its genome contains six genes in order 5′ L-H-F-M-P-N 3′ and displays specific evolutional features (Fakri et al., 2016; Ratta et al., 2016; Bao et al., 2017; Ma et al., 2017; Ma et al., 2018). Surprisingly, PPRV lineage IV strain Kurdistan/2011 in transmission trials indicated that pigs and wild boar can serve as PPRV reservoirs (Schulz et al., 2018). A change of a single amino acid in a nonhuman morbillivirus is sufficient to overcome the barrier between human and animals (Abdullah et al., 2018). These phenomena imply that PPRV might expand its susceptible host range to some degree.

Interferon (IFN) response is the first defense line against viral infection. IFNs are cytokines with broad-spectrum antitumor, antiviral, immune adjuvant and immunomodulatory effects. They are classified into three different groups, type I (IFN-α, IFN-β, IFN-δ, and others), type II (IFN-γ) and type III (IFN-λ1, IFN-λ2 and IFN-λ3) IFNs (Grandvaux et al., 2002; Zhou et al., 2018). The initial stage in the type I IFN response is the production of IFN-β, which usually occurs soon after viral infection, and requires various transcription factors to bind to the regulatory domains of the IFN-β promoter (Cavalieri et al., 1977; Goodbourn et al., 1985; Wathelet et al., 1998). However, PPRV is able to inhibit IFN-β production, depending on its V and C proteins (Sanz Bernardo et al., 2017). Type I and III IFNs play important roles in antiviral responses which are involved with many immune signal pathways (Ank et al., 2006; Pott and Stockinger, 2017; Ingle et al., 2018). Classical Janus kinase signal transducerand activator of transcription (JAK-STAT)pathway is commonly mediated by IFNs (Raftery and Stevenson, 2017; Zan et al., 2017). Once activated, STAT1 and STAT2 are phosphorylated and bind to IFN regulatory factors (IRFs), and subsequently translocate to the nuclues, leading to the transcription of hundreds IFN-stimulated genes (ISGs) which cooperatively establish an anti-viral state against various types of viruses (Schneider et al., 2014). ISGs are the ultimate effectors of IFN-mediated antiviral responses.

* Corresponding authors at: X.X. Ma, Biomedical Research Center, Northwest Minzu University, Lanzhou, China.
** Corresponding to: Y. Shang, State Key Laboratory of Veterinary Etiological Biology, Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou, Gansu, PR China.
E-mail addresses: maxiaoxia956@163.com (X.-x. Ma), shangyoujun@caas.cn (Y. Shang).
[1] The two authors have equal contributions to this work.

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Regulated upon activation normal T cells expressed and secreted (RANTES) is a C−C β chemokine (68 a.a.) is a selective chemo attractant of human monocytes and lymphocytes and induces the migration of monocytes, eosinophils, T cells, NK cells, mast cells, and basophils to sites of inflammation and infection (Hellewell and Morganti-Kossmann, 2012). It has been recognized that PPRV infection can impair IFN-mediated immune defense, but little information about PPRV-host interactions and therapeutic development of IFN-based treatment against PPRV infection. Here, we comprehensively assessed the role of endogenous and the therapeutic IFNs on PPRV infection in HEK293T cells. We found that the basal JAK-STAT cascade is effective in restraining PPRV infection. Furthermore, PPRV is sensitive to inhibition by two types of IFNs in cell culture model. Our results strengthen the evidence of essential roles of IFN pathway in protecting the host against viral infection.

2. Materials and methods

2.1. Cell line and virus

HEK293T cells were cultured in Dulbecco's modified Eagles's medium (DMEM, Minhai, Lanzhou, China) containing 10% heat-inactivated fetal bovine serum (FBS; Minhai, Lanzhou) in 5% CO2 at 37 °C in a humidified incubator. Live-attenuated PPRV vaccine strain Nig75/1 was obtained from China Institute of Veterinary Drug Control.

2.2. Reagents

Type I human recombinant IFN-α-2b, IFN-β and IFN-λ3 (Invitrogen, USA) were dissolved in PBS with 0.1%BSA with a final concentration of 1×10^6 IU/mL, 1×10^6 IU/mL and 100 ng/μL respectively. Stocks of Jak inhibitor I (Santa Cruz Biotech,CA) was dissolved in DMSO (Sigma-Aldrich, StLouis, MO, USA) with a final concentration of 1.62×10^4 μmoL/L.

2.3. Infection of PPRV for HEK 293 T cells

For quantification of PPRV replication, HEK 293 T cells were seeded into 6-well cell culture plates (Costar, Corning, USA) and grow for 24 h until cell layers were 3×10^5 cells/well. The culture medium was removed. The cell layers were washed twice with 1 mL PBS, and 1 mL serum-free DMEM medium containing PPRV was added into the cell layers and incubated for 1 h at 37 °C with 5%CO_2 to allow efficient infection, followed by washing twice with PBS to remove PPRV in cell supernatant. Finally, 3 mL culture medium containing 10% FBS were added into the treated cell layers and cultured for 0 h, 12 h, 24 h, 36 h and 48 h at 37 °C with 5%CO_2.

2.4. Quantification of PPRV replication in HEK 293 T cells

According to our previous report (Chang et al., 2018), total intracellular or extracellular (secreted) RNA was isolated by using the TRIzol reagent (Invitrogen, USA)and quantified by Biospectrometer (Eppendorf, Germany) according to the manufacturer's protocol.cDNA was made from total RNA using a cDNA Synthesis Kit (Promega, USA) with random hexamer primers. qRT-PCR of PPRV RNA and genes of interest were performed with a All-in-One™ qPCR Mix (GeneCopoeia,lnc. USA), according to the manufacturer's instructions with the CFX96™ Real-Time system (Bio-Rad Laboratories,Inc.USA).Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a housekeeping gene to normalize (relative) gene expression using the $2^{-\Delta\Delta CT}$(ΔCT_{sample}-$\Delta CT_{control}$) formula. All primers used in this study are as follows:

PPRV-F: 5'-CTGAATACCAACATTGAG-3′;

PRPRV-R: 5'-GAGGAACTTAATCTTATCG-3′;

GAPDH-F: 5'-CTCTGGTAAAGTGGATATTGT-3′;

GAPDH-R: 5'-GGTGGAATCATATTGGAACA-3′.

2.5. Enzyme-linked immunosorbent assay (ELISA)

Supernatant was analyzed for IFN-β, IFN-λ_2 and IFN-λ3 secretion by ELISA kit (LVYE Biotechnology, Jiangsu, China) according to manufacturer's instructions. The absorbance was measured at 450 nm in an automatic microplate reader. Results were calculated based on a standard curve.

2.6. Cytotoxicity assay

Potential cytotoxic effects of IFN-α-2b, IFN-β, IFN-λ3 and JAK-inhibitor I on HEK293T cells were tested using the Cell Counting Kit-8 (Biodragon, Beijing, China). HEK293T cells were seeded in 96-well microplates (Costar, Coring, New York, USA) for 24 h. Then, the medium was replaced with 100 μL of 10% FBS DMEM supplemented with various concentration of IFN-α-2b (10 IU/mL, 100 IU/mL 1000 IU/ml), IFN-β (10 IU/mL、100 IU/mL、1000 IU/mL 10,000 IU/mL), IFN-λ3 (10 ng/mL、100 ng/mL、1000 ng/mL) and JAK-I inhibitor (1 μmol/L,5 μmol/L and 10 μmol/L), respectively. DMEM +10%FBS without IFN-α-2b, IFN-β, IFN-λ3 or JAK-I inhibitor was represented as control. Followed by incubating cells for 48 h. Finally, CCK-8 assay was performed according to the manufacturer's recommendation (http://www.solarbio.com).In brief, 10 μL of CCK-8 stock solution were added to each well and incubated at 37 °C for 2 h. Optical density at 450 nm was measured for each well. The percentage of cell viability was calculated as follows:

$$\%viability = \frac{OD_{agent}}{OD_{control}} \times 100\%$$

2.7. Exogenous IFN treatment

According to the previous reports (PMID:29844362, PMID:28558073), cells were seeded in 6-well plates in DMEM complemented with 10% FBS and cultured for 12 h. Followed by treatment with IFN-α-2b (0, 10 IU/mL, 100 IU/mL, 1000 IU/mL), IFN-β (0, 10 IU/mL、100 IU/mL、1000 IU/mL 10,000 IU/mL) or IFN-λ3 (0, 10 ng/mL, 100 ng/mL, 1000 ng/mL for 12 h. Finally, the treated HEK293T cells were infected with PPRV and incubated for different hours.

2.8. Statistical analysis

Statistical analysis was performed using the unpaired, nonparametric test (Mann-Whitney test; GraphPad Prism software 6.0, GraphPad Software Inc.). p values<0.05 was considered statistically significant.

3. Results

3.1. Types I and III IFN genes activated by PPRV infection

Relative RNA levels of IFN-α, IFN-β, IFN-γ, IL29 (IFN-λ1) and IL28 (IFN-λ3) genes were tested at 0, 12, 24, 36 and 48 h post-infection. An effective replication was shown by an increase in intracellular RNA level (Supplementary Fig.S1). As shown in Fig. 1A, the transcription of IFN-β gene was slightly triggered at 24 h post-infection with PPRV. Importantly, at 36 and 48 h post-infection with PPRV, transcription of IFN-β gene was notably increased by 2.6 ± 1.5(p<0.001) and 5.9 ± 4.9 (p<0.001) folds, respectively. IFN-λ_2 was slightly triggered at 36 h, while increased by 3.5 ± 2.5 (P<0.001) folds at 48 h post-infection with PPRV respectively (Fig. 1B). Transcription of IFN-λ_3 was significantly enhanced by 5.8 ± 4.8 (P<0.001) and 21.8 ± 20.8 (P<0.001) folds at 36 and 48 h post-infection with PPRV, respectively (Fig. 1C).The transcription levels of IFN-α and IFN-γ genes were

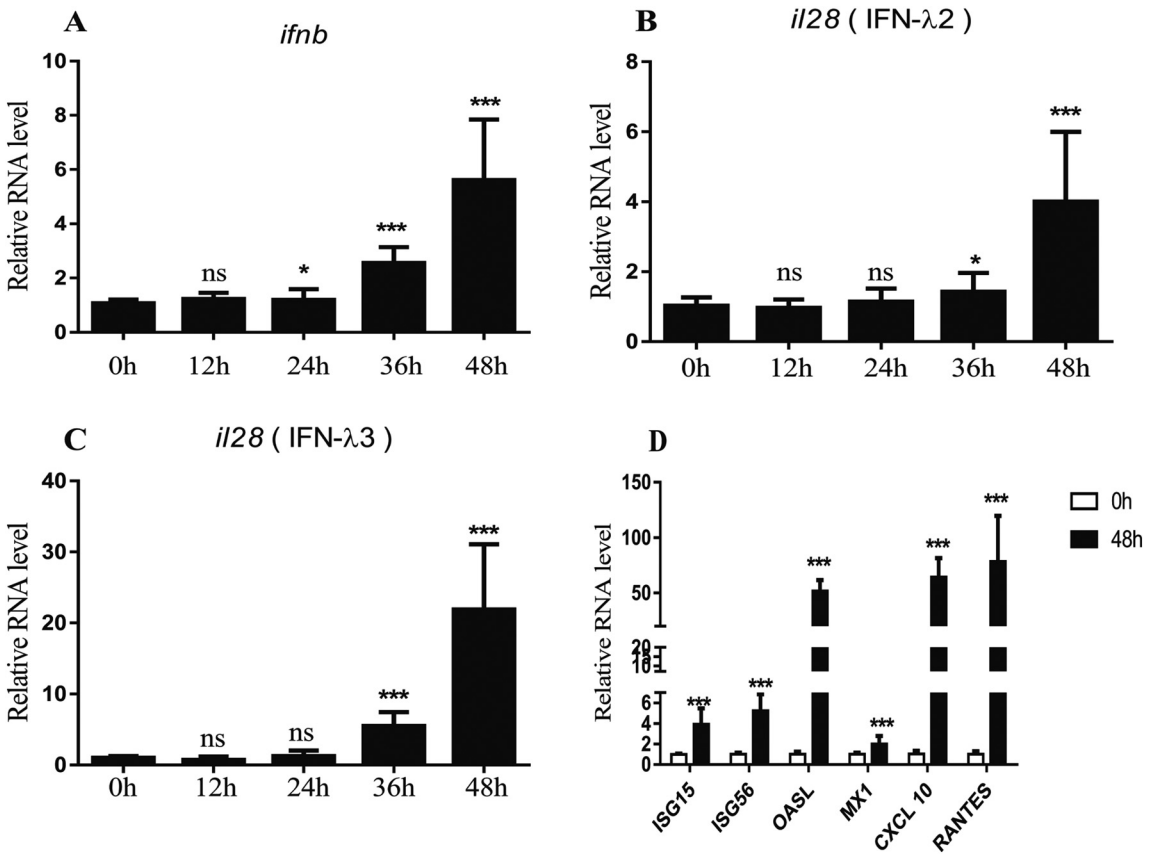

Fig. 1. PPRV infection regulates the expression IFN genes and IFN-stimulated genes (ISGs) inHEK293T cells. HEK293T cells were infected with 1 MOI PPRV, relative RNA levels of (**A**) IFN-α (**B**) IFN-λ2(**C**) IFN-λ3 genes were quantified at 12, 24, 36, 48 h post-infection. (D) Relative RNA levels of ISGs were quantified at 48 h post-infection. Data were normalized to GAPDH and presented as means ± SEM. (n = 3 independent experiments with each of twice replicates; *P<0.05; **P<0.01; ***P< 0.001).

undetectable (data not shown).Together, these results suggest that PPRV infection can preferentially activate the transcription of IFN-β, IFN-λ_2 and IFN-λ3 in HEK293T cells. In addition, we found that some ISGs were significantly induced in HEK293T cells by PPRV infection, including ISG15, ISG56, OSAL, MX1, CXCL 10 and RANTES (Fig. 1D).

3.2. The increased expression of IFN genes was not sufficient to limit PPRV replication

To examine whether the increased expression of IFN genes results in inhibition of PPRV replication, we collected the conditioned medium (supernatant) derived from control (non-infected by PPRV) or PPRV-infected cells which were cultured for 48 h. Then, we performed IFN production bioassay by adding the conditioned medium into PPRV-infected HEK293T cells. As shown in Fig. 2 , treatment with the supernatant from PPRV-infected cells was not sufficient to inhibit PPRV replication. Furthermore, no significant differences in IFN-β, IFN-λ_2 and IFN-λ3 protein level were observed in the supernatant of these cells (Supplementary Fig.S2).

To rule out the possibility that endogenous IFN produced (if any) following PPRV infection is sufficient to restrict PPRV replication, we investigated whether the inhibition of JAK proteins, the downstream elements of IFN receptor, influences PPRV replication. Treatment of JAK I inhibitor at 1, 5 and 10 μM had no effect on PPRV replication (Fig. 2B). At those concentrations, the drug influenced the cell viability as determined by MTT assay (Fig. S3A). Collectively, our results demonstrated that the increased expression of IFN genes during PPRV infection did not result in IFN production and consequently, was not sufficient to limit PPRV replication.

3.3. PPRV is sensitive to exogenous IFN treatment

Subsequently, we estimated the role of exogenous IFN treatment in PPRV replication in the target cells. Here, IFN-α-2b, IFN-β and IFN-λ3 of different concentrations were used for treatment of HEK293T cells for 12 h, prior to PPRV infection, respectively. We found either IFN-α 2b, IFN-β or IFN-λ3 was able to inhibit viral replication in a dose-dependent manner (Fig. 3A-3C). Importantly, the concentration of 1000 IU/mL for IFN-α-2b, 10,000 IU/mL for IFN-β, or 1000 ng/mL for IFN-λ3 significantly inhibits PPRV replication (p<0.001).

To profile the antiviral dynamics of IFNs against PPRV infection, IFN-α-2b at the concentration (1000 IU/mL), 10,000 IU/mL for IFN-β, or 1000 ng/mL for IFN-λ3 was treated to PPRV-infected HEK293T cells for 12, 24, 36 and 48 h, respectively. The PPRV-infected HEK293T cells without treatment of IFN served as control. We found that IFN-α-2b and IFN-λ3 were able to inhibit PPRV replication at 24 h with an optimal antiviral potency at 48 h, while IFN-β was able to inhibit PPRV replication at 36 h with an optimal antiviral potency at 48 h, compared to control (Fig. 3D). As for the transcription of some ISGs post IFN-α-2b treatment, ISG15, ISG56 and CXCL-10 were significantly enhanced at 48 h, while those of OASL, MX1 and RANTES were only slightly changed, compare to control (Fig. 3E). Collectively, these results suggest that IFN-α, IFN-β and IFN-λ3 effectively inhibit PPRV replication in cell culture model system.

3.4. The JAK-STAT signaling pathway mediates the anti-PPRV effect of exogenous IFNs

Although no functional level of IFN is induced by PPRV infection, we delineated the role of exogenous IFNs signaling in regulating PPRV

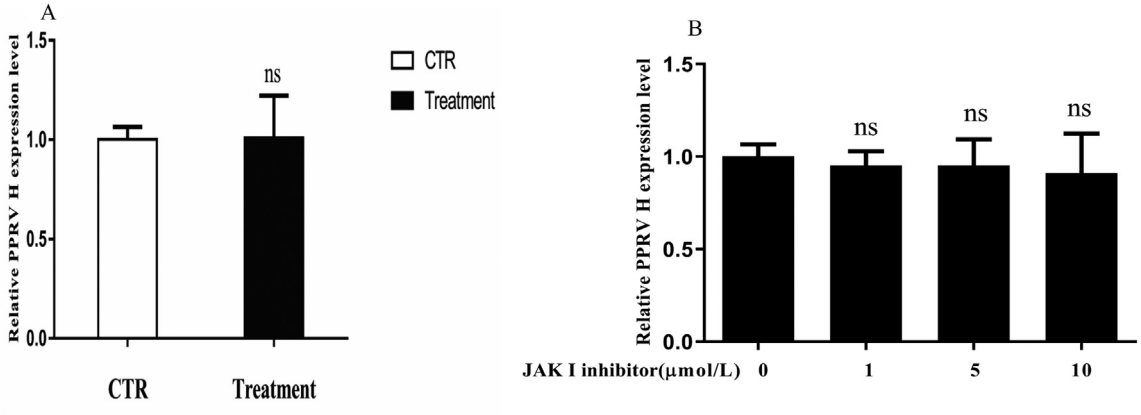

Fig. 2. Increased expression of IFN genes was insufficient to restrict PPRV replication. (A) IFN production bioassay was performed in HEK293T cells infected with PPRV. Conditioned medium derived from HEK293T cells which were treated with PPRV infection for 48 h, (B) HEK293T cells were treated with PPRV infection for 48 h followed by treated with 1, 5 or 10 μM JAK I inhibitor, relative RNA levels of PPRV H gene was quantified. (n = 3 independent experiments with each 2–3 replicates). Data were presented as means ± SEM., *P<0.05; **P<0.01; ***P<0.001.

replication. JAK I inhibitor, which can effectively inhibit JAKI-induced STAT1 and STAT2 phosphorylation, was employed. As expected, treatment of JAK I inhibitor at 1, 5 and 10 μM efficiently blocked activation of IFN signaling pathway mediated by IFN-α-2b, IFN-β and IFN-λ3 , which in turn attenuated the antiviral activity of IFN-α-2b, IFN-β and IFN-λ3 in HEK293T cells (Fig. 4). These data clearly indicate an important role of JAK-STAT pathway in mediating the anti-PPRV effects of IFNs.

4. Discussion

It is currently believed that PPRV, like other morbilliviruses, is able to evade immune response of host, even though IFNs play key roles in antiviral responses to viral infection (Reid and Charleston, 2014). The viral accessory proteins (V and C) can impair the induction of IFN-β following PPRV infection of cultured cells (Sanz Bernardo et al., 2017). In our study, we further confirm that the production of IFN-α and IFN-λ3 is affected in post PPRV infection in HEK293T cells, but the transcription of IFN-α and IFN-λ3 can be stimulated after PPRV infection. Once PPRV infects the target cells, viral genome, like other RNA viruses, is rapidly recognized by pattern recognition receptors (PRRs) of host cells, subsequently triggering cascade responses for activating transcriptions of IFN genes (IFN-α andIFN-λ3). Type I IFN confers fast antiviral response, while type III IFN display antiviral protection in slow acting manners (Pervolaraki et al., 2018). This is consistent with our study that the transcription of IFN-β is faster than that of IL28. This result suggests that transcription efficiencies of types I and III IFN play a role in the difference of antiviral responses between type I and type III IFNs.

Although transcription of type I and III IFNs was observed post PPRV infection, we do not detect endogenous IFN productions derived from PPRV-infected HEK293T cells. ISG products are highly effective at controlling and resisting pathogens. Current understanding of PPRV and other Paramyxoviridae have been heavily assumed that lSG15, ISG56 and (CXCL-10) showed significant response and play a significant role in ISG-mediated resistance to virus infection (Nazar et al., 1997;

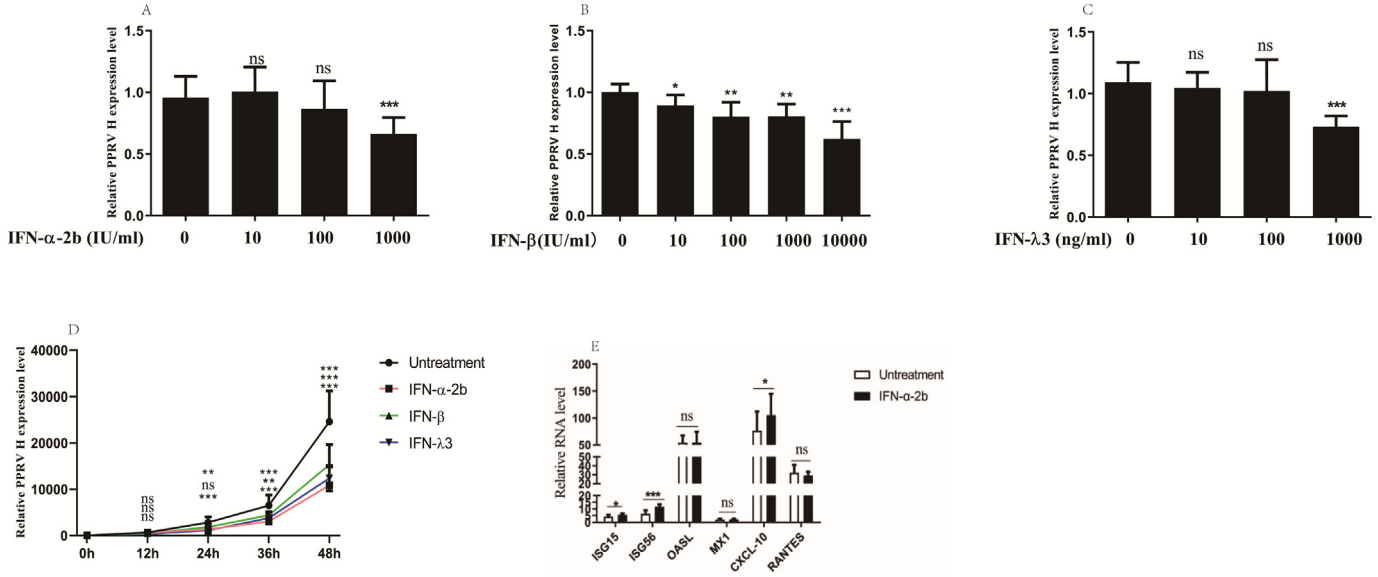

Fig. 3. PPRV was sensitive to exogenous IFN-α-2b or IFN-λ3 treatment. IFN production bioassay was performed in HEK293T cells infected with PPRV. Anti-viral activity of therapeutic (A) IFN-α-2b, (B) IFN-λ3 were quantified after treatment for 12 h in PPRV infectedHEK293T cells (C) HEK293T cells were treated with IFN-α-2b for 48 h, (D) IFN-α-2b (1000 IU/mL), IFN-β (10,000 IU/mL), or IFN-λ3 (1000 ng/mL) were treated to PPRV-infected HEK293T cells for 12, 24, 36 and 48 h, respectively, relative RNA levels of PPRV H gene was quantified. (E) Relative RNA levels of ISG genes were quantified after treatment of IFN-α-2b for 12 h in PPRV infected HEK293T cells (n = 3 independent experiments with each 2–3 replicates). Data were presented as means ± SEM., *P<0.05; **P<0.01; ***P<0.001.

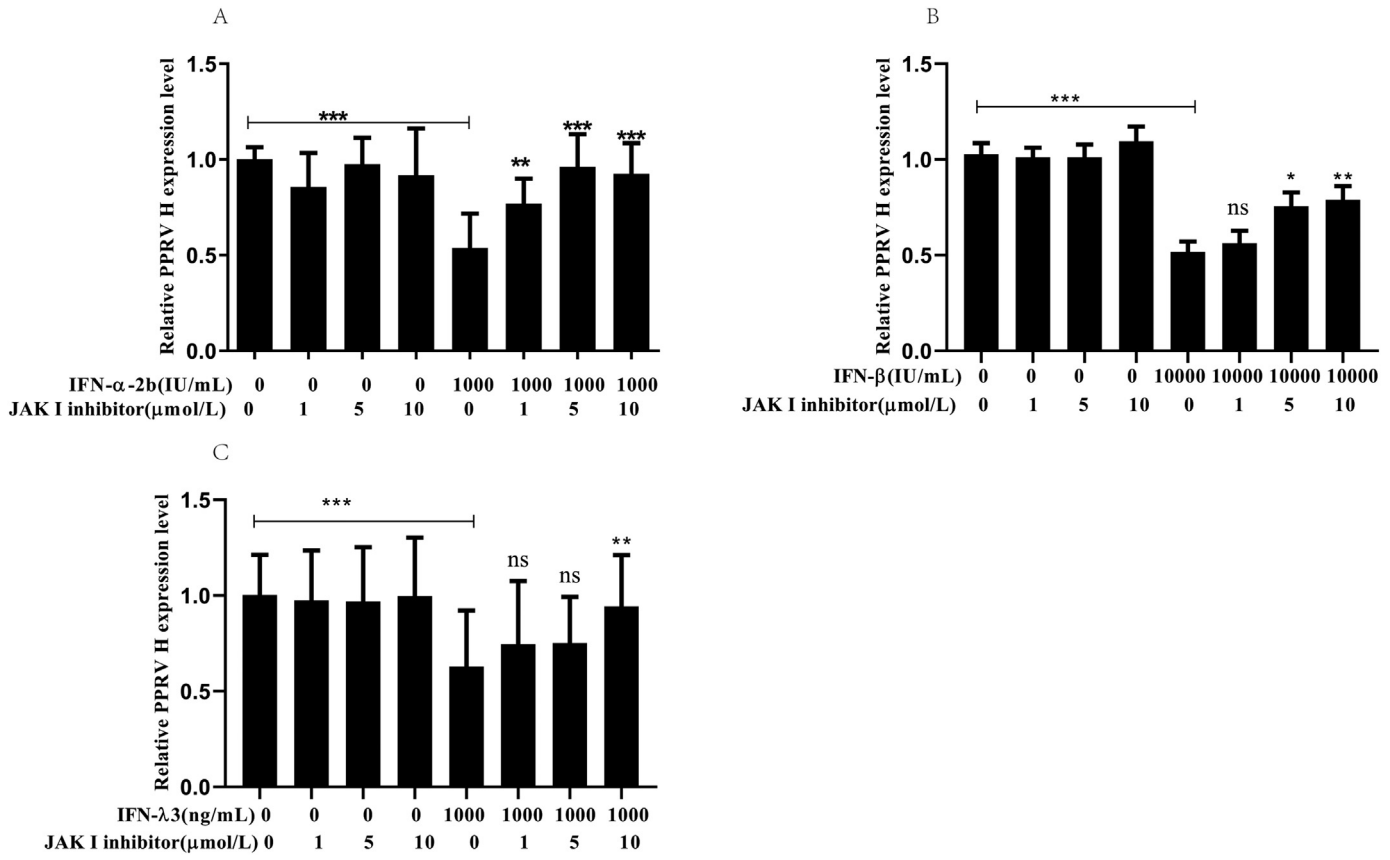

Fig. 4. Inhibition of JAK-STAT signaling abrogates the anti-PPRV activity of IFN-α-2b. HEK293T cells were pre-treated with 5 or 10 μM JAK I inhibitor and (A) 1000 IU/mL IFN-α-2b, (B) 10,000 IU/mL IFN-β, (C) or 1000 ng/mL IFN-λ3, followed by infected with 1 MOI PPRV relative, RNA levels of PPRV H gene was quantified (n = 3 independent experiments with each 2–3 replicates). Data were presented as means ± SEM., $^{**}P<0.01$; $^{***}P<0.001$.

Vanquri and Farber, 1994; Wani et al., 2018). Although obvious production of endogenous IFNs (types I and III) were not detected from PPRV-infected cells, transcription of some ISG genes were significantly enhanced (Fig. 1D). This result indicates that PPRV infection is effective at inhibiting production of IFN (types I and III), but the triggering transcription of ISG genes reflects that a few amount of types I and III IFNs is produced after PPRV infecting HEK293T cells. Among the triggered transcription of ISGs, the transcription levels of OASL, CXCL 10 and RANTES were higher than those of ISG15, ISG56 and MX1 (Fig. 1 D), suggesting that OASL, CXCL 10 and RANTES play important roles in antiviral reaction to PPRV infection. Mx 1, ISG15 and ISG56 are broadly inhibitory and acts prior to genome replication at an early postentry step of the virus life circle (Farrell et al., 1979; Fensterl and Sen, 2011; Verhelst et al., 2013). The three types of ISGs were significantly stimulated after PPRV infection, but their transcription might be limited by PPRV to some degree. The protective effects of AOAS/RNase L are generally more pronounced for RNA viruses compared with DNA viruses. This probably reflects the variety of antiviral mediators that detect different viral species. CXCL 10 is an IFN-inducible chemokine which recruits activated T and NK cells to the site of infection (Chen et al., 2006). RANTES stimulates T cells *via* two discrete pathways, first is a transient Ca2 + mobilization by GPCR-mediated pathway leading to cell polarization and migration, second is a sustained Ca2 + surge dependent on protein tyrosine kinase (PTK)-mediated pathway resulting in multiple cellular responses including T cell proliferation or apoptosis (Albert et al., 2017). Although PPRV infection is able to impair production of types I and III IFNs, the triggering production of CXCL 10 and RANTES could increase cellular responses derived from T cell and NK cell. The treatment of IFN-α-2b to HEK293T cells prior to PPRV infection can strongly stimulate transcription of CXCL 10 for resisting PPRV infection (Fig. 2E), suggesting that IFN-α-2b signaling pathway is involved in cellular responses, therefore IFN-α-2b enhances antiviral responses mediated by ISG15 / ISG56 and cellular responses mediated by CXCL 10 for resisting PPRV infection.

In conclusions, our study describes the role of both endogenous and exogenous IFN in PPRV infection, as well as the role of both basal and activated IFN signaling in limiting RV infection. The knowledge could contribute to the better understanding of PPRV-host interactions and therapeutic development.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2019.103981.

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Conflict of interest statement

The authors declare that the research was con-ducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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