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Pancreatic adenocarcinoma upregulated factor (PAUF) confers resistance to pancreatic cancer cells against oncolytic parvovirus H-1 infection through IFNA receptor-mediated signaling

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ABSTRACT

Pancreatic adenocarcinoma upregulated factor (PAUF), a novel oncogene, plays a crucial role in the development of pancreatic cancer, including its metastasis and proliferation. Therefore, PAUF-expressing pancreatic cancer cells could be important targets for oncolytic virus-mediated treatment. Panc-1 cells expressing PAUF (Panc-PAUF) showed relative resistance to parvovirus H-1 infection compared with Panc-1 cells expressing an empty vector (Panc-Vec). Of interest, expression of type I IFN-α receptor (IFNAR) was higher in Panc-PAUF cells than in Panc-Vec cells. Increased expression of IFNAR in turn increased the activation of Stat1 and Tyk2 in Panc-PAUF cells compared with that in Panc-Vec cells. Suppression of Tyk2 and Stat1, which are important downstream molecules for IFN-α signaling, sensitized pancreatic cancer cells to parvovirus H-1-mediated apoptosis. Further, constitutive suppression of PAUF sensitized Bxpc3 pancreatic cancer cells to parvovirus H-1 infection. Taken together, these results suggested that PAUF conferred resistance to pancreatic cancer cells against oncolytic parvovirus H-1 infection through IFNAR-mediated signaling.

1. Introduction

Pancreatic cancer has extremely poor prognosis, with a 5-year survival rate of <5% [1,2]. The only potential curative treatment for pancreatic cancer is surgery; however, only 10%–20% patients with pancreatic cancer are candidates for surgery at the time of presentation. Therefore, novel tumor-specific biomarkers and genetic pathways that may identify potential diagnostic and therapeutic targets are needed to prevent the late diagnosis, decrease the aggressiveness, and increase the sensitivity of pancreatic cancer to existing therapies [3]. Previously, we showed that pancreatic cancer cells express a novel secretory protein called pancreatic adenocarcinoma upregulated factor (PAUF). Introduction of PAUF into Chinese hamster ovary (CHO) cells induces tumor formation in xenografted nude mice [4]. Further, we showed that PAUF expression upregulates CXCR4 expression, which eventually enhances the metastasis of pancreatic cancer cells [5]. Moreover, PAUF contributes to the oncogenesis of pancreatic cells by upregulating β-catenin [6,7].

Autonomous parvovirus H-1 comprises a small, non-enveloped icosahedral particle containing a single-stranded DNA genome of ~5 kb [8]. Parvovirus H-1 has received attention because of its oncotropic and oncotoxic properties [9]. Its lytic cycle leads to tumor cell death via an apoptotic or a lysosomal pathway [10]. A recent study showed that administration of parvovirus H-1 prolongs the survival of rats with glioma cell transplants in the brain, without any cytotoxic effect on other tissues [11]. Clinical phase I/IIa trials have been performed in patients with progressive primary or recurrent glioblastoma multiforme, the most malignant type of glial tumor [12]. In pancreatic cancers, IFN-γ released by immune cells accelerates parvovirus H-1-mediated oncolysis [13]. Parvovirus H-1 uses cellular SMAD4, a transcription factor that binds to

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the viral P4 promoter, for efficient replication in pancreatic cancer cells [14].

Type I IFN-α receptor (IFNAR), which belongs to type II cytokine receptor superfamily, contains 2 subunits: IFNAR1 and IFNAR2 [15]. This heterodimeric complex interacts with IFN-α and IFN-β, resulting in the phosphorylation of Tyk2 and Jak1 bound to IFNAR1 and IFNAR2, respectively [16]. Further, this complex phosphorylates Stat proteins (Stat1 and Stat2) at specific tyrosine residues, resulting in the formation of a Stat1/2 heterodimer based on SH2/phosphotyrosine interactions. Stat1/2 heterodimer facilitates its association with IRF9 to form an active heterotrimeric transcription factor called IFN-stimulated gene factor 3 (ISGF3). ISGF3 targets specific sequences such as IFN-stimulated response element and IFN-γ-activated sequence in the promoters of IFN-stimulated genes to elicit an antiviral response [17].

Because our previous studies showed that PAUF played a crucial role in the metastasis and proliferation of pancreatic cancer cells, we assumed that PAUF-expressing pancreatic cancer cells could be useful targets for treatment with oncolytic parvovirus H-1. However, we observed that these cells were resistant to parvovirus H-1 infection. Further, we demonstrated that PAUF established an antiviral response through IFNAR-mediated signaling.

2. Materials and methods

2.1. Cell culture and virus amplification

Panc-1 cells stably expressing PAUF (Panc-PAUF) and corresponding control cells (Panc-Vec) were cultured in DMEM supplemented with 10% FBS, 1% penicillin, 1% streptomycin, and 500 μg/ml G418 at 37 °C in 5% CO_2. Bxpc3 pancreatic cancer cells with stable knockdown of PAUF (Bxpc-shPAUF cells) and corresponding control cells (Bxpc-shCon cells) were cultured under the same condition. Parvovirus H-1 was purchased from American Type Culture Collection (Manassas, VA) and was propagated in normal rat kidney cells. The virus was purified as described previously [18], and viral titer was expressed as $TCID_{50}$/ml.

2.2. Reagents and antibodies

IFN-α was purchased from R&D Systems (Minneapolis, MN). Anti-β-actin and horseradish peroxidase (HRP)-conjugated secondary antibodies for immunoblotting were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-IFNAR1 and anti-IFNγR antibodies were obtained from Abcam (Cambridge, MA). Antibodies against Tyk2, Stat1, phosphorylated Tyk2 and Stat1, and poly-ADP-ribose polymerase (PARP) were purchased from Cell Signaling (Danvers, MA). Polyclonal anti-parvovirus H-1 antibodies were obtained by immunizing a rabbit 3 times with purified parvovirus H-1.

2.3. Western blotting

Cells were harvested and were lysed in lysis buffer (150 mM NaCl, 1% NP-40, and 50 mM Tris–HCl [pH 7.5]) containing 0.1 mM Na_2VO_3, 1 mM NaF, and protease inhibitors (Sigma). For immunoblotting, proteins from whole cell lysates were separated on 10% or 12% SDS-PAGE and were transferred onto nitrocellulose membranes. Primary antibodies were used at 1:1000 or 1:2000 dilution, and HRP-conjugated secondary antibodies were used at 1:2000 dilution in 5% nonfat dry milk. After final washing, the nitrocellulose membranes were exposed to an enhanced chemiluminescence reagent and were photographed using ImageQuant LAS 4000 Mini (GE Healthcare, Cleveland, OH, USA).

2.4. Transfection with short interfering RNA

Before transfection with short interfering RNAs (siRNAs), cells were trypsinized and were incubated overnight until they reached 60%–70% confluence. For transfection, Tyk2 siRNAs (200 nM; Bioneer, Daejeon, Korea; sense, 5′-UCU CAC CUC UUC CCA UUC C [dTdT]-3′; antisense, 5′-GGA AUG GGA AGA GGU GAG A[dTdT]-3′), Stat1 siRNAs (200 nM; Bioneer; sense, 5′-ACU UUG CUG UAA CCC UGU A[dTdT]-3′; antisense, 5′-UAC AGG GUU ACA GCA AAG U [dTdT]-3′), and negative control siRNAs (Bioneer) [19] were mixed with Lipofectamine 2000 (Invitrogen, Carlsbad, CA). The cells were incubated with the transfection mixture for 6 h and were rinsed with RPMI-1640 containing 10% FBS. Next, the cells were incubated for 48 h.

2.5. RT-PCR analysis

Total RNA was extracted from cells by using RNeasy Protect Cell Mini Kit (Qiagen, Valencia, CA), according to the manufacturer's instructions. Next, 3 μg of the total RNA was reverse transcribed to cDNA by using Superscript II Reverse Transcriptase (Invitrogen), and PCR was performed using specific primers described previously [20]. The cDNA obtained was diluted, and PCR was performed for optimized number of cycles. β-Actin mRNA was measured as an internal standard. The PCR products were electrophoresed on 1.5% agarose and were visualized by staining the gel with ethidium bromide.

2.6. Immunofluorescence

Cells were fixed with 4% paraformaldehyde for 15 min, permeabilized with cold acetone for 15 min, blocked with 10% goat serum for 30 min, and treated with primary antibodies (1:100 dilution) for 30 min at room temperature. After incubation, the cells were washed extensively with PBS, incubated with Alexa Fluor 514-conjugated goat anti-mouse antibody (1:500 dilution; Molecular Probes, Eugene, OR) in PBS for 30 min at room temperature, and washed 3 times with PBS. The stained cells were mounted using PBS containing 10% glycerol and were photographed using LMS510 confocal microscope (Zeiss, Oberkochen, Germany).

2.7. Statistical analysis

Data are presented as mean ± standard error of the mean. Student's *t*-test was used for statistical analysis, and $P < 0.05$ was considered significant.

3. Results

3.1. PAUF confers resistance against oncolytic parvovirus H-1 infection

Because PAUF plays a crucial role in the development of pancreatic cancer (e.g., proliferation of pancreatic cancer cells through the expression of β-catenin [6,7] and metastasis through the upregulation of CXCR4 [21]), PAUF-expressing pancreatic cancer cells are important targets for oncolytic virus-mediated treatment. We herein introduced onclolytic H-1 parvovirus because this virus has been used for recurrent glioblastoma multiforme in clinical trials [12]. Panc-PAUF and Panc-Vec cells were infected with parvovirus H-1 (MOI = 1). The cells were observed under light microscope at 24 and 48 h after the infection, and the number of viable cells was measured using trypan blue exclusion assay. Panc-PAUF cells were relatively resistant to oncolytic parvovirus H-1

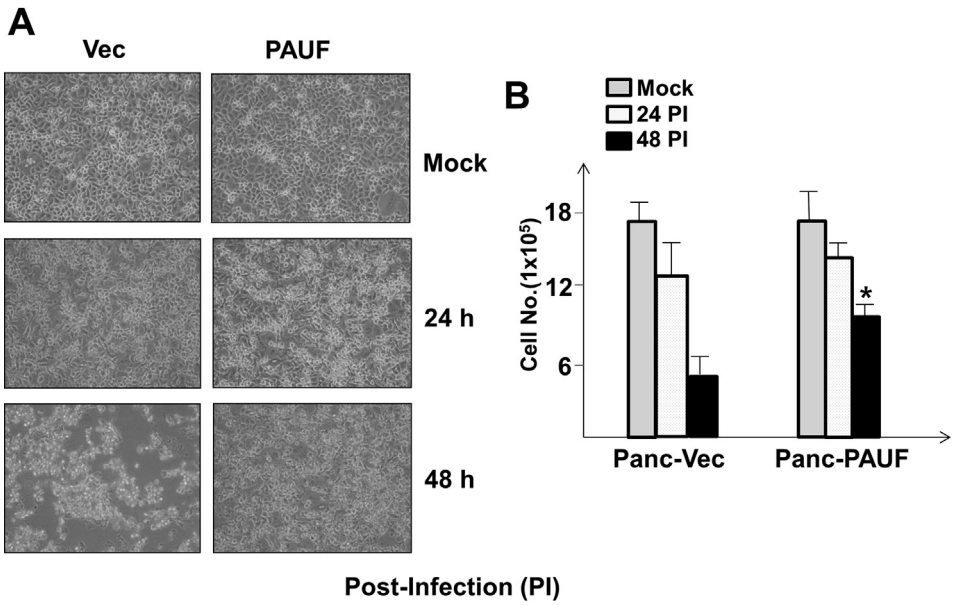

Fig. 1. PAUF expression confers resistance to Panc-1 cells against parvovirus H-1 infection. (A, B) Panc-Vec and Panc-PAUF cells were infected with parvovirus H-1 (MOI = 1) and were examined under light microscope at 24 and 48 h after the infection. Live cells were evaluated using trypan blue exclusion assay at 48 h after the infection. Results are an average of triplicate wells, and error bars indicate SEM. (*$P < 0.05$, Panc-Vec *vs* Panc-PAUF at 48 h post-infection).

infection compared with Panc-Vec cells (Fig. 1A). At 48 h after infection, cultures of Panc-PAUF cells showed more number of viable cells (~2-fold) than cultures of Panc-Vec cells (Fig. 1B). However, it was unclear how PAUF elicited an antiviral response against parvovirus H-1 in Panc-1 cells.

3.2. PAUF enhances the expression of IFNAR in Panc-1 cells

To determine how PAUF induced resistance against parvovirus H-1 infection, we assessed the IFNAR signaling, a well-known signaling pathway in antiviral response. IFNAR expression was higher in Panc-

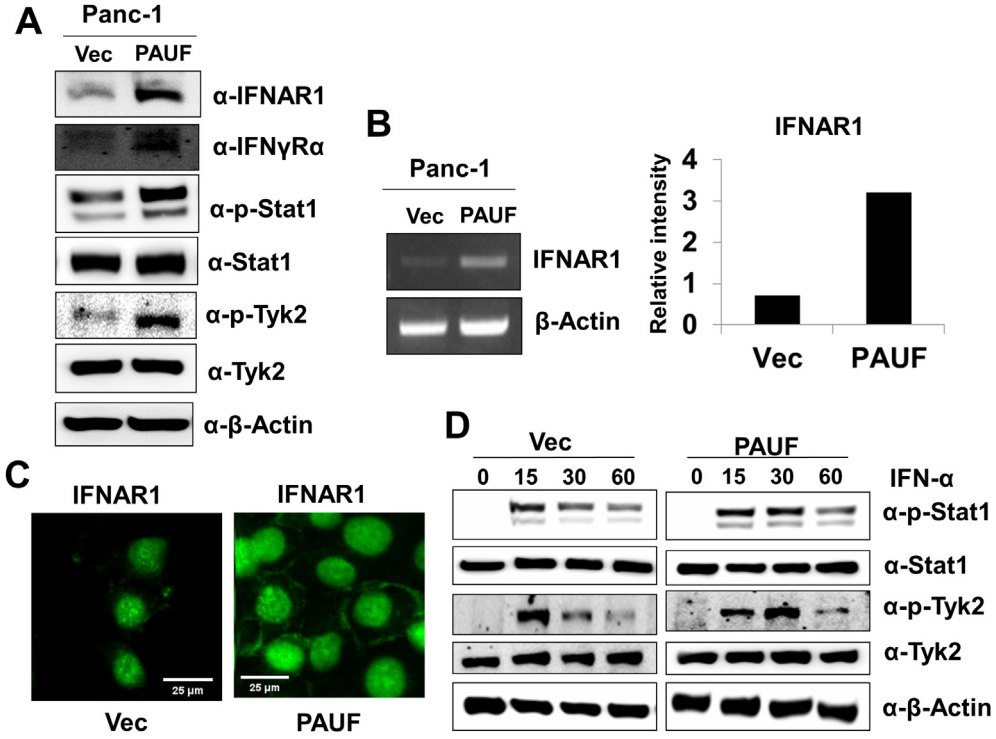

Fig. 2. PAUF increases IFNAR1 expression, leading to the amplification of type I IFN signaling. (A) Cell lysates of Panc-Vec and Panc-PAUF cells were electrophoresed on 10% SDS-PAGE. IFNAR1, IFNγR, phospho-Stat1, Stat1, phospho-Tyk2, and Tyk2 were immunoblotted using corresponding antibodies. (B) Total RNA isolated from Panc-Vec and Panc-PAUF cells was examined using RT-PCR. *IFNAR1* was amplified using specific primers, and the amplification products were visualized on 1.5% agarose gels stained with ethidium bromide. β-Actin was used as an internal control. Band intensities were measured using Multi Gauge version 2.1 (Fuji, Tokyo, Japan). *IFNAR1* mRNA levels were expressed relative to β-actin mRNA levels. (C) Panc-Vec and Panc-PAUF cells were incubated with anti-IFNAR1 antibody after fixation and permeabilization. IFNAR1 present on cell surface was visualized using confocal microscopy after staining with Alex Flour 514-conjugated goat anti-mouse antibody. (D) Panc-Vec and Panc-PAUF cells were treated with IFN-α (1000 unit/ml) for 60 min and were harvested at 15, 30, and 60 min after the treatment. Levels of phosphorylated Stat1 and Tyk2 were detected using corresponding antibodies.

PAUF cells than in Panc-Vec cells (Fig. 2A). Further, confocal microscopy confirmed that Panc-PAUF cells showed higher IFNAR1 expression than Panc-Vec cells (Fig. 2C). Panc-PAUF cells also showed slightly higher expression of IFN-γ receptor than Panc-Vec cells (Fig. 2A). Additionally, we examined endogenous levels of phosphorylated Stat1 and Tyk2 in Panc-Vec and Panc-PAUF cells. Levels of phosphorylated Stat1 and Tyk2 levels were higher in Panc-PAUF cells than in Panc-Vec cells (Fig. 2A). We have a question that increased expression of IFNAR1 in Panc-PAUF cells may be attributed to increased transcription of *IFNAR1*. Next, total RNA was extracted from Panc-Vec and Panc-PAUF cells, and PCR was performed using IFNAR1-specific primers after synthesizing cDNA to answer this question. Levels of *IFNAR1* transcripts were higher in Panc-PAUF cells than in Panc-Vec cells (Fig. 2B), confirming that the increase in IFNAR1 protein levels in Panc-PAUF cells was because of increased transcription of *IFNAR1*. Next, we examined how Panc-PAUF cells with increased IFNAR1 levels responded to IFN-α compared with Panc-Vec cells. Both Panc-PAUF and Panc-Vec cells were treated with IFN-α after 12 h of serum starvation and were harvested at 15, 30, and 60 min after IFN-α treatment. Levels of phosphorylated Stat1 and Tyk2, the known downstream molecules of IFN-α signaling, rapidly declined in Panc-Vec cells at 30 min after IFN-α treatment; however, those were maintained in Panc-PAUF cells at the same time point (Fig. 2D). This result indicated that PAUF enhanced IFNAR expression, which in turn amplified IFN-α signaling for a longer period.

3.3. Suppression of Tyk2 or Stat1 sensitizes Panc-PAUF cells to parvovirus H-1-mediated apoptosis

Previous studies have shown that Tyk2 is essential for stable cell surface expression of IFNAR1 and that Tyk2 stabilizes IFNAR1 by interacting with it in the basal condition [22]. Therefore, we determined whether suppression of Tyk2 expression decreased cell surface expression of IFNAR1 in Panc-PAUF cells, thus sensitizing them to parvovirus H-1 infection. Suppression of Tyk2 expression with its siRNA decreased IFNAR1 levels in Panc-PAUF cells (Fig. 3A). Next, Panc-PAUF cells were treated with parvovirus H-1 under Tyk2 suppression condition. In the absence of Tyk2, Panc-PAUF cells allowed the replication of parvovirus H-1, leading to sensitization of apoptosis (Fig. 3B and C). After infection with parvovirus H-1, Panc-PAUF cells treated with control siRNA showed better survival (~2.5-fold) than Panc-PAUF cell treated with Tyk2 siRNA (Fig. 3B). Taken together, these results suggested that PAUF increased IFNAR1 expression by activating Tyk2, thus maintaining the antiviral response.

Although the levels of phosphorylated Stat1 were higher in Panc-PAUF cells than in Panc-Vec cells, it was unclear whether PAUF contributed to the antiviral response in a Stat1-independent manner. Suppression of Stat1 by its siRNA reduced IFNAR1 expression in Panc-PAUF cells (Fig. 3D). Further, suppression of Stat1 increased the susceptibility of Panc-PAUF cells to parvovirus H-1 infection (Fig. 3E), as indicated by increased viral replication and cleaved PARP fragments in Panc-PAUF cells treated with Stat1 siRNA (Fig. 3E). This result indicated that PAUF-mediated antiviral response was dependent on Stat1.

3.4. Constitutive inhibition of PAUF enhances parvovirus H-1-mediated oncolysis of Bxpc3 pancreatic cancer cells

Bxpc3 pancreatic cancer cells highly express endogenous PAUF. In our previous study, we generated Bxpc3 cells with constitutively suppressed PAUF (Bxpc-shPAUF cells) and

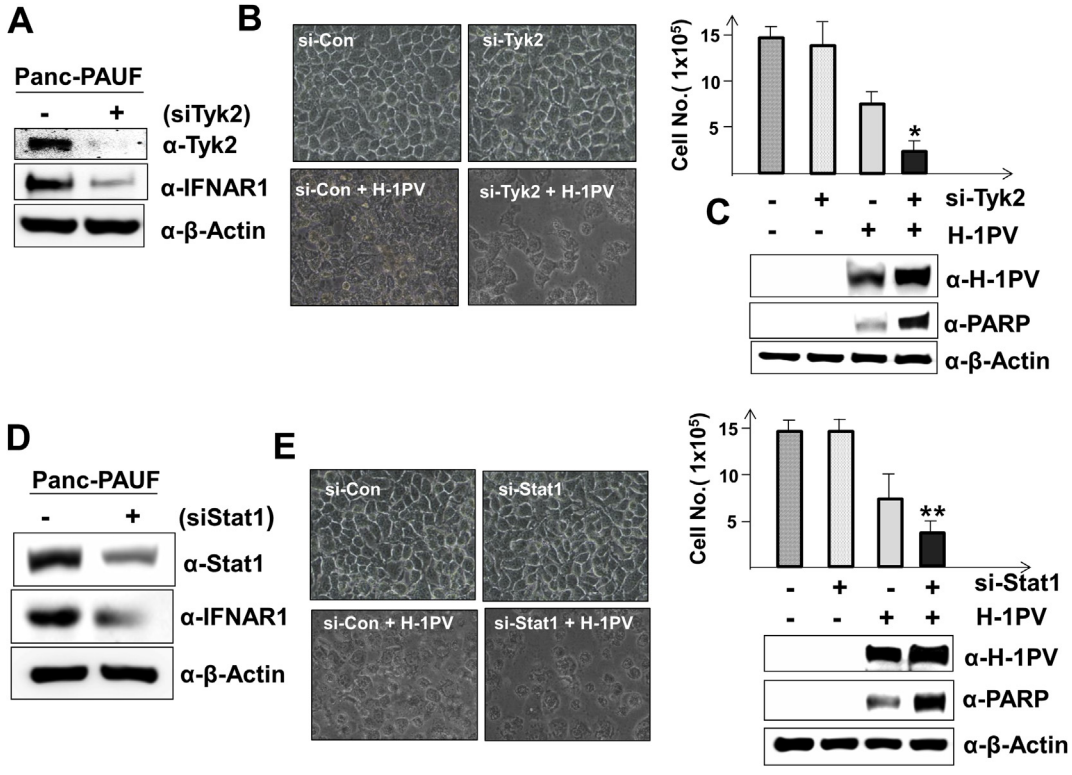

Fig. 3. Suppression of Tyk2 or Stat1 decreases IFNAR1 expression and sensitizes the cells to parvovirus H-1-mediated apoptosis. (A, D) Panc-PAUF cells were treated with Tyk2 siRNAs, Stat1 siRNAs, and control siRNAs for 48 h. The cells were then harvested, and levels of Tyk2, Stat1, and IFNAR1 were detected using corresponding antibodies. (B, C, E) Panc-PAUF cells were infected with parvovirus H-1 (MOI = 1) at 24 h after Tyk2 or Stat1 siRNA treatment and were observed under light microscope at 24 and 48 h after the infection. Live cells were evaluated using trypan blue exclusion assay at 48 h after the infection. Results are an average of triplicate wells, and error bars indicate SEM. (*$P < 0.05$, Control siRNA + H-1 *vs* Tyk2 siRNA + H-1 at 48 h post-infection). (**$P < 0.05$, Control siRNA + H-1 *vs* Stat1 siRNA + H-1 at 48 h post-infection). Cell lysates were harvested 48 h post-infection for immunoblotting. H-1 capsid protein and cleaved PARP fragments were detected using corresponding antibodies at 48 h after the infection.

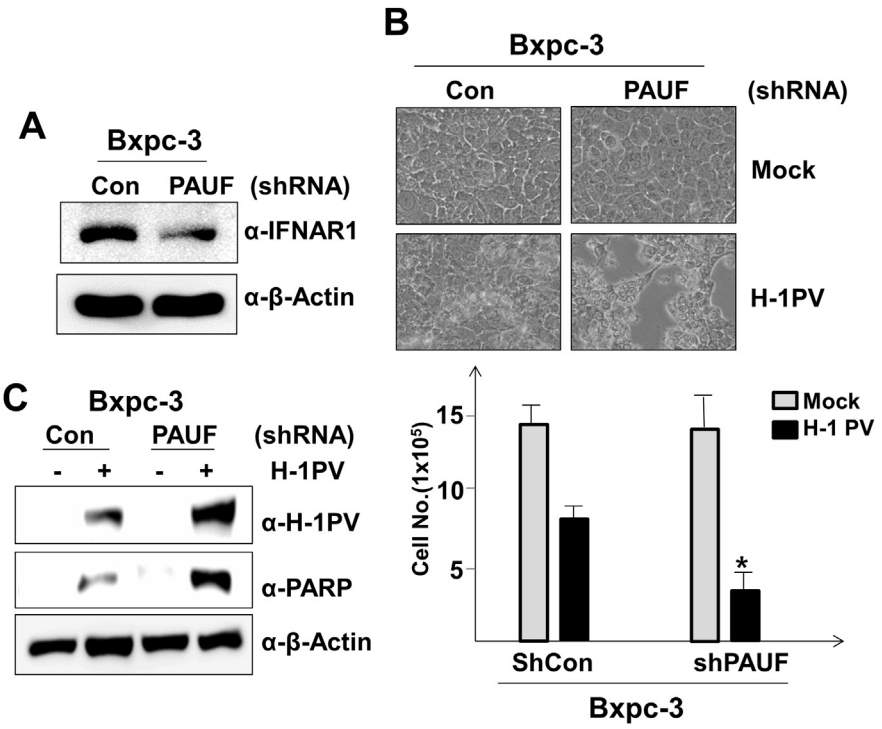

Fig. 4. Suppression of PAUF sensitizes Bxpc3 pancreatic cancer cells to parvovirus H-1-mediated apoptosis. (A) Lysates of Bxpc-shPAUF and Bxpc-shCon cells were electrophoresed on 10% SDS-PAGE. IFNAR1 levels were detected using anti-IFNAR1 antibody. (B, C) Cells were infected with parvovirus H-1 (MOI = 1) and were observed under light microscope at 24 and 48 h after the infection. Live cells were evaluated using trypan blue exclusion assay at 48 h after the infection. Results are an average of triplicate wells, and error bars indicate SEM. (*$P < 0.05$, Bxpc-shCon *vs* Bxpc-shPAUF). H-1 capsid protein and cleaved PARP fragments were detected using corresponding antibodies at 48 h after the infection.

corresponding control cells (Bxpc-shCon cells) [4]. In the present study, Bxpc-shPAUF cells showed lower IFNAR expression than Bxpc-shCon cells, indicating that PAUF expression was closely associated with increased IFNAR expression (Fig. 4A). We used Bxpc-shPAUF cells to determine whether PAUF possessed antiviral activity against parvovirus H-1. Treatment of Bxpc-shPAUF and Bxpc-shCon cells with parvovirus H-1 showed that Bxpc-shPAUF cells were more sensitive to the virus than Bxpc-shCon cells (Fig. 4B). Further, increased viral replication and cleaved PARP fragments were detected in Bxpc-shPAUF cells (Fig. 4C), confirming that PAUF played an important role in eliciting an antiviral response.

4. Discussion

Our previous studies have shown that PAUF is a secretory protein [4]. Moreover, X-ray crystallization studies have shown that it is a mammalian lectin protein [21]. Additional studies have reported that PAUF functions as an endogenous ligand of Toll-like receptor 2 (TLR2) and TLR4 by screening extracellular domain receptor pools [21]. PAUF–TLR2 interaction induces ERK phosphorylation and activates IKK-β-mediated TPL2/MEK/ERK signaling pathway through TLR2 [21]. TLR2-mediated ERK activation by PAUF increases the expression of protumorigenic cytokines RANTES and MIF in THP-1 cells [21]. Although TLR2 or TLR4 expression is restricted to myeloid immune cells, recent studies have detected TLR expression in epithelial tumor cells. A strong correlation has been observed between ubiquitous TLR4 and MyD88 expression and paclitaxel chemoresistance in human epithelial ovarian cancer cells, which increases tumor survival by producing proinflammatory cytokines and by activating TLR4 signaling [23]. Therefore, we hypothesize that interaction of PAUF with TLR2 or TLR4 on the surface of Panc-1 cells might induce type I IFN, thus enhancing IFNAR expression. To test this hypothesis, we are investigating TLR2 or TLR4 or expression on the surface of Panc-PAUF cells. We observed that PAUF increased the *IFNAR* transcription, which involved transcription factors such as Stat1, Stat3, IRF1, and IRF7-A (www.genecards.org). We thus have an assignment to elucidate the mechanism of PAUF-mediated upregulation of *IFNAR1* transcription.

Several studies have shown that IFN/Stat1 pathway may facilitate tumor cell growth. Other studies have reported that resistance to ionizing radiation and IFNs is associated with constitutive overexpression of the IFN/Stat1 pathway in radioresistant tumor cells [24]. Recent studies have also shown that constitutive overexpression of Stat1 protects tumor cells from genotoxic stress such as treatment with doxorubicin [25] or cisplatin [26]. Because overexpression of the IFN/Stat1 pathway is associated with poor prognosis of different cancers, IFN-related genes may serve as prognostic markers in patients with breast cancer who are resistant to adjuvant chemotherapy [27]. Our recent study also showed that cancer upregulated gene 2, a novel oncogene, activated Stat1, thus enhancing metastasis and resistance to doxorubicin [28]. We thus propose that Stat1 activation via PAUF/IFNAR-mediated signaling in pancreatic cancer cells might contribute to their metastasis and resistance to anticancer drugs, eventually leading to oncogenesis. However, further studies are needed to explore the role of PAUF-mediated Stat1 activation in tumor formation.

Conflict of interest

None.

Acknowledgments

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Transparency document

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