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Borna disease virus nucleoprotein inhibits type I interferon induction through the interferon regulatory factor 7 pathway

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ABSTRACT

The expression of type I interferon (IFN) is one of the most potent innate defences against viral infection in higher vertebrates. Borna disease virus (BDV) establishes persistent, noncytolytic infections in animals and in cultured cells. Early studies have shown that the BDV phosphoprotein can inhibit the activation of type I IFN through the TBK1–IRF3 pathway. The function of the BDV nucleoprotein in the inhibition of IFN activity is not yet clear. In this study, we demonstrated IRF7 activation and increased IFN-α/β expression in a BDV-persistently infected human oligodendroglia cell line following RNA interference-mediated BDV nucleoprotein silencing. Furthermore, we showed that BDV nucleoprotein prevented the nuclear localisation of IRF7 and inhibited endogenous IFN induction by poly(I:C), coxsackie virus B3 and IFN-β. Our findings provide evidence for a previously undescribed mechanism by which the BDV nucleoprotein inhibits type I IFN expression by interfering with the IRF7 pathway.

1. Introduction

The expression of type I interferon (IFN-α/β) is one of the most potent innate defences in higher vertebrates against infection with viruses such as coxsackie virus B and herpes simplex virus. Type I interferons can also be induced by poly(I:C) and CpG DNA [1]. The type I IFN system plays an important role in innate resistance to many viruses by inducing direct and indirect antiviral effects. Interferon regulatory factors (IRFs) are a family of transcription factors involved in regulating type I IFN genes and other genes that participate in the early antiviral host response. IRF3 and IRF7 are essential transcriptional factors resulting in the induction of IFN-α/β transcription following viral infection. Activated IRF3 and IRF7 undergo nuclear translocation and subsequently bind to IRF-binding elements [i.e., positive regulatory domains (PRDs) I and III and PRD-like elements (PRD-LEs)] in the IFN-α/β promoter region [2]. Recent studies have shown that IRF7 is the master regulator of IFN gene expression [3,4].

The IFN-α/β can be induced by viral infection. However, IFN induction and production are inhibited by many viruses, including negative-sense single-stranded RNA viruses, such as measles virus, rinderpest virus, vesicular stomatitis virus, Ebola virus, rabies virus (RABV), Nipah virus, and respiratory syncytial virus (RSV). These viruses have developed extraordinarily diverse strategies to impair IFN signalling or to counteract cellular antiviral effectors [5]. The nucleoproteins of lymphocytic choriomeningitis virus (LCMV), classical swine fever virus (CSFV), respiratory syncytial virus (RSV) and rabies virus are involved in the inhibition of IFN expression in host cells [6–9].

Borna disease virus (BDV) is a neurotropic, negative-stranded RNA virus that causes a nonsuppurative meningoencephalomyelitis in a wide range of animals and establishes persistent, noncytolytic infections [10,11]. The nucleoprotein, phosphoprotein and X protein of BDV are the essential constituent elements of the polymerase complex [12]. The nucleoprotein is the most abundant protein in BDV-infected cells and tissues and mediates the cellular immune response [11,13]. BDV phosphoprotein is an essential cofactor of the viral RNA-dependent RNA polymerase [14]. The X protein is a potential negative factor for polymerase activation [15]. Early studies have shown that exogenous IFN does not appear to influence persistent BDV infection in Madin–Daby canine kidney cells (MDCK) and C6 cells and that phosphoprotein associates with and inhibits the TBK1–IRF3 activation pathway in MDCK cells [16]. However, it is unclear whether the BDV nucleoprotein is involved in the regulation of natural immunity.

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In this study, we designed small interfering RNA (siRNA) plasmids and a BDV protein expression plasmid to evaluate the function of the BDV nucleoprotein in the inhibition of type I IFN expression in oligodendroglia (OL) cells. The results showed that BDV nucleoprotein prevented the nuclear localisation of IRF7 and inhibited endogenous type I IFN induction by poly(I:C), coxsackie virus B3 and IFN-β. Our findings provide evidence for a previously undescribed mechanism by which the BDV nucleoprotein inhibits type I IFN expression by interfering with the IRF7 pathway.

2. Materials and methods

2.1. Cells and viruses

BDV strain 1766, human oligodendroglial (OL) cells, and BDV-persistently infected OL (OL/BDV) cells were kindly donated by Professor Kazuyoshi Ikuta, Department of Virology, Osaka University, Japan. Coxsackie virus B3 (CVB3) Nancy strain was provided by the Department of Microbiology, Harbin Medical University, China. OL and OL/BDV cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% and 2% foetal bovine serum, respectively, and 100 U/mL penicillin/streptomycin at 37 °C and 5% CO_2.

2.2. Plasmids

We constructed the plasmids pmCherry-IRF7 and peGFP-BDV-N for this study. The IRF7 open reading frame was inserted into the multiple cloning site of pmCherry-N1 (TaKaRa, Japan). IRF7 fused with red fluorescent protein (RFP) mCherry was expressed by pmCherry-IRF7. The BDV nucleoprotein open reading frame was inserted into the multiple cloning site of peGFP-N1 (TaKaRa). BDV nucleoprotein fused with enhanced green fluorescent protein (EGFP) could be expressed by peGFP-BDV-N. All plasmids used in this study were confirmed by sequencing. The empty peGFP-N1 plasmid was used as a control.

2.3. RNA interference (RNAi)

The small interfering RNA (siRNA) targeting the mRNA of BDV nucleoprotein was inserted into a plasmid by GenePharma (Shanghai, China). Two siRNA plasmids (sRNAi-N-219 5′-GCCTAGCCTTG TGTTTCTATG-3′ and sRNAi-N-699 5′-GCAGATGACCACGTACAC-TAC-3′) were introduced into OL/BDV cells with Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. A sRNAi-NC plasmid with an unrelated sequence was used as a negative control. Cell cultures were continued for 48 h before detection. The silencing efficiency was monitored by real-time PCR for mRNA levels. OL/BDV cells were co-transfected with pmCherry-IRF7 plasmid and siRNA expression plasmids. Twenty-four hours later, the location of IRF7 was detected in the transfected cells.

2.4. Transfection of plasmids

A 24-well plate was seeded with 5×10^4 cells/well in antibiotic-free DMEM medium supplemented with 5% FCS. After 24 h incubation, cells were transfected with BDV nucleoprotein expression plasmids or empty peGFP-N1 using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. The cultures were continued for 24 h before cells were exposed to treatments with poly(I:C) (100 μg/mL; Sigma, USA) and CVB3 (MOI 0.5). Total RNA was extracted from cells at 4 h post-treatment. OL cells were co-transfected with pmCherry-IRF7 plasmid and BDV nucleoprotein expression plasmids. Twenty-four hours later, the transfected cells were treated with poly(I:C), CVB3 or IFN-β for 4 h. The expression and location of fluorescence was observed by inverted fluorescence microscopy.

2.5. Quantitative reverse transcriptase (RT)-PCR

Total RNA isolated from cells was prepared using TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. Total RNA was reverse transcribed into cDNA using M-MLV reverse transcriptase (Promega, USA) and Oligo dT^{18} (TaKaRa). Quantitative PCR was performed on a LightCycle 2.0 (Roche) using SYBR Premix Ex Taq (TaKaRa) according to the manufacturer's protocol. Primers for the measurement of human type I IFN, BDV nucleoprotein and human GAPDH mRNA levels were as follows: IFN-α (F: 5′-GAACTCTACCAGCAGCT-3′, R: 5′-CAGATAGAGAGTGATTC-3′), IFN-β (F: 5′-AAGGCCAAGGAGTACAGTC-3′, R: 5′-AGTTTCGGGGTAACCTG-3′), BDV nucleoprotein (F: 5′-GGTTTAAAACTATGATGGCAGCCTTA-3′, R: 5′-GTGGATTAACATCTGGAGTAGTGTAGC-3'), GAPDH (F: 5′-ACCACAGTACATGCGATCAC-3′, R: 5′-TCCACCACCCTGTTGCTGTA-3′). Analysis of relative change in gene expression was calculated according to the $2^{-\Delta\Delta ct}$ method using the GAPDH gene as the control.

2.6. Statistical analysis

All values are presented as the mean and standard error of the mean (SEM). Statistical analysis was performed using SigmaStat 3.0 (Systat Software, Richmond, CA). The Student's *t* test was used to evaluate the differences between two groups. A *P* value of <0.05 was considered statistically significant. All experiments were repeated at least three times.

3. Results

3.1. BDV inhibits expression of type I IFN in persistently infected OL cells

The level of IFN-α/β mRNA in OL/BDV cells was compared with that in normal OL cells by quantitative-PCR, and the GAPDH gene was used as an internal control. The IFN-α/β level was significantly lower in OL/BDV cells (Fig. 1A), indicating that persistent BDV infection inhibited expression of type I IFN.

It has previously been shown that BDV phosphoprotein counteracts TBK1-dependent IFN-β expression and therefore the establishment of antiviral activity in cells [16]. To identify the function of the BDV nucleoprotein in the inhibition of IFN-α/β expression, we designed siRNA plasmids targeting the nucleoprotein and introduced these plasmids into OL/BDV cells. Forty-eight hours later, we measured the BDV nucleoprotein mRNA, protein and IFN-α/β mRNA levels. The BDV nucleoprotein (N) mRNA level was significantly reduced in OL/BDV cells following siRNA plasmid (sRNAi-N-219 and sRNAi-N-699) transfection, and the IFN-α/β mRNA level was increased compared with control siRNA (sRNAi-NC) transfected OL/BDV cells (Fig. 1B,C,F and G). These results suggest that BDV nucleoprotein is also involved in the resistance to IFN.

Previous studies have shown that IRF3 and IRF7 are key factors in IFN-α/β induction [2–4] and that BDV phosphoprotein counteracts the TBK1–IRF3 pathway to inhibit IFN activation [16]. To measure the activation of IRF7 in OL/BDV cells, a pmCherry-IRF7 plasmid and the siRNA plasmids were co-transfected into OL/BDV cells. Forty-eight hours later, the nuclear localisation of IRF7 was increased in OL/BDV cells co-transfected with siRNA plasmids compared with control cells as analysed by fluorescence microscopy (Fig. 1E and H).

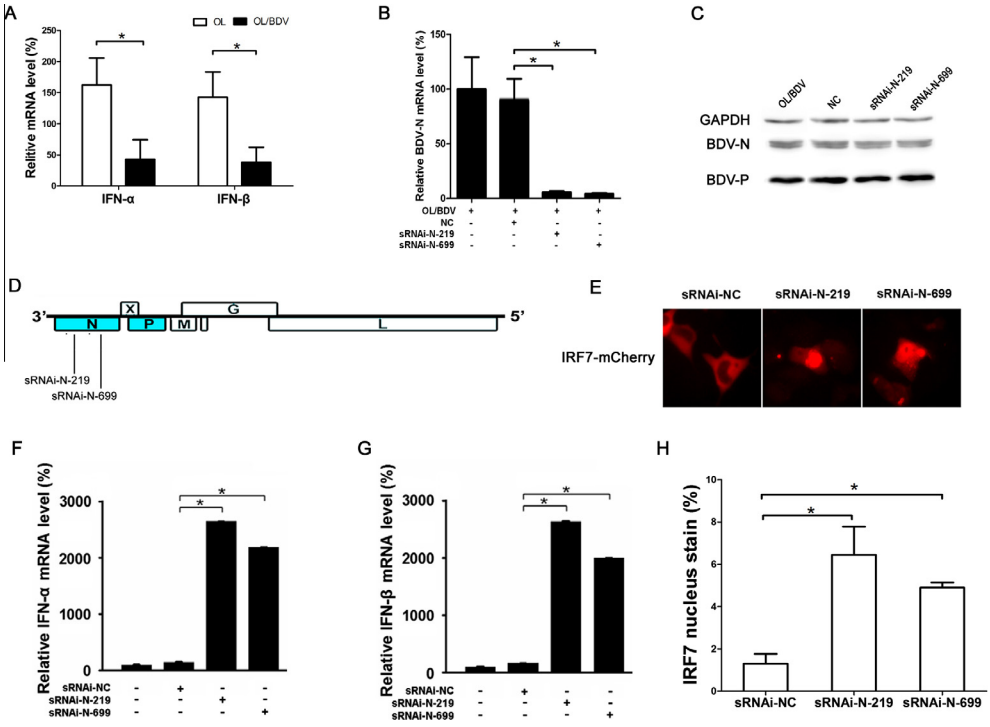

Fig. 1. BDV proteins inhibit expression of type I IFN in OL/BDV cells. (A) IFN-α/β mRNA levels were lower in OL/BDV than in OL cells. (B,C) Nucleoprotein mRNA and protein levels were measured in OL/BDV cells at 48 h after RNAi plasmid transfection; note the drop compared to NC controls. (F) IFN-α level was significantly increased in OL/BDV cells transfected with RNAi plasmids compared to NC controls. (G) IFN-β level was significantly increased in OL/BDV cells transfected with RNAi plasmids compared to NC controls. (E,G) mCherry was used to determine IRF7 expression and localisation by fluorescence microscopy (400×); note that the siRNA plasmid transfection increased IRF7 nuclear localisation. $^{*}p < 0.05$.

3.2. BDV nucleoprotein inhibits expression of type I IFN in OL cells transfected with the BDV nucleoprotein expression vector

The BDV nucleoprotein and phosphoprotein are the important constituent elements of the polymerase complex; therefore, the transcription and translation of these proteins are related to BDV replication [12]. To analyse the effect of BDV nucleoprotein on IFN expression independent of the nucleoprotein effect on replication, we introduced peGFP-BDV-N (N) into OL cells and used peGFP-N1 as a negative control (NC). Forty-eight hours later, we collected the cell lysates and used anti-BDV-nucleoprotein monoclonal antibodies to detect BDV nucleoprotein (Fig. 2A and B).

OL cells were transfected with peGFP-BDV-N (N) and treated with poly(I:C), CVB3 or IFN-β as IFN inducers 48 h later. We then measured the mRNA level of IFN-α/β at 4 h after treatment (Fig. 2C–F). Considerably less IFN-α/β was induced in OL cells transfected with peGFP-BDV-N (N) compared with control peGFP-N1 (NC) treated cells ($p < 0.05$), suggesting that BDV nucleoprotein also inhibits IFN.

3.3. BDV nucleoprotein inhibits nuclear localisation of IRF7 in OL cells

IRF7 plays an important role in IFN induction, particularly in IFN-receptor-mediated IFN amplification, which plays an important role in resistance to viral infection [3]. Therefore, we co-transfected OL cells with peGFP-BDV-N (N) and pmCherry-IRF7 to verify the interaction between the nucleoprotein and IRF7. Forty-eight hours later, poly(I:C), CVB3 or IFN-β were used to treat the co-transfected OL cells. The nuclear localisation of IRF7 was analysed by fluorescence microscopy four hours after treatment (Fig. 3A). Nuclear localisation of IRF7 in OL cells over-expressing BDV nucleoprotein was significantly lower than that in the peGFP-N1 group (NC) (Fig. 3B). This suggests that BDV nucleoprotein can inhibit IRF7 activation.

4. Discussion

Virus infection can increase the expression of type I IFN in host cells. However, some viruses have several mechanisms to inhibit IFN production. For example, EBV BGLF4 kinase inhibits the IRF3 signalling pathway [17]; West Nile virus non-structural proteins inhibit Toll-like receptor 3 signal transduction [18]; RABV nucleoprotein and phosphoprotein inhibit the phosphorylation of IRF3 [9,19]; and BDV phosphoprotein can inhibit the activation of IRF3 [16].

In this study, RNAi was used to analyse the function of the BDV nucleoprotein in type I IFN induction. We found a reduction of type I IFN expression and IRF7 activation in OL/BDV cells. RNAi silencing of BDV nucleoprotein expression in OL/BDV can increase IRF7 nuclear localisation and IFN-α/β production. These results indicate that BDV inhibits the IFN signalling pathway in host cells through a new BDV nucleoprotein-mediated mechanism. However, the siRNAs targeting N protein were introduced into BDV persistently infected OL cells in which TBK1 pathway is consistently inhibited by the P protein. Accordingly, the reconstructed plasmid expressing BDV N protein was used in further experiments to exclude the influence of irrelevant proteins. The results showed that BDV nucleoprotein significantly inhibited IRF7 activation and type I IFN production. We infer that during the establishment of a persistent infection, BDV phosphoprotein and nucleoprotein are both involved in the inhibition of IFN production.

Many viruses can inhibit IFN function in host cells. Some RNA virus nucleoproteins also inhibit IFN production. For example, CSFV nucleoprotein inhibits expression of IFN by hydrolysis of IRF3 and IRF7 [20,21]. Arenaviridae nucleoproteins inhibit NF-κB activation by combining with Inhibitor of κB kinase ε (IKKε) [22,23]. Lymphocytic choriomeningitis virus nucleoprotein inhibits IFN responses [6]. Human RSV nucleoprotein and inclusion bodies inhibit the melanoma differentiation-associated protein 5

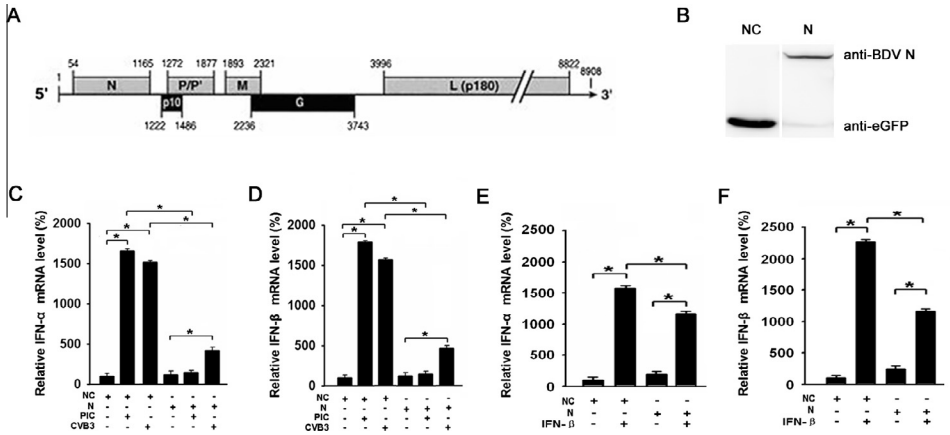

Fig. 2. Type I IFN was inhibited in OL cells transfected with BDV Nucleoprotein (N) expression plasmid. (A) BDV genome structure. (B) Expression of BDV N was detected by mouse monoclonal antibody in OL cells 48 h after transfection. (C,D) Expression of IFN-α/β was significantly decreased in OL cells after transfection with N plasmid compared to peGFP-N1 controls (NC) at 4 h after poly(I:C) (PIC) or CVB3 treatment. (E,F) Expression of IFN-α/β was significantly decreased in OL cells after transfection with N plasmid at 4 h after IFN-β treatment.

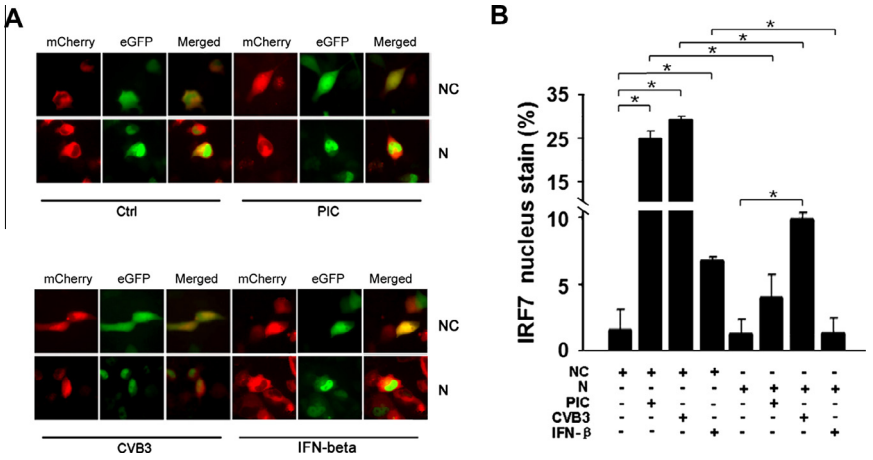

Fig. 3. BDV Nucleoprotein (N) inhibited activation of IRF7 in OL cells. (A) GFP was used to assess N expression, and mCherry was used to determine IRF7 expression and localisation by fluorescence microscopy (400×). (B) N transfection decreased IRF7 nuclear localisation in OL cells 4 h after poly(I:C) (PIC), CVB3 or IFN-β treatment. $^{*}p < 0.05$.

(MDA5)- and mitochondrial antiviral-signalling protein (MAVS)-mediated innate immune response [8]. RABV nucleoprotein functions to evade the activity of host IFN and chemokines [9].

Among the nine members of the IRF family, IRF3 and IRF7 are essential transcriptional factors for inducing IFN-α/β expression following viral infection. IRF3 is constitutively expressed in a variety of cells and is mainly involved in the induction of IFN during early virus infection. However, IRF3 does not affect the amplification and antiviral activity of endogenous IFN in IFN-treated cells [24]. RNA virus infection activates the retinoic acid inducible gene I (RIG-I) receptor and TLR3 pathways in host cells. This increases IFN-β production thereby activating IRF7 and induces a large amount of IFN-α/β. The induced IRF7 plays a key role in positive feedback amplification of IFN. Some studies have shown that IRF7 plays a particularly important role in type I IFN induction [3,4].

Early studies showed that the endogenous irritants poly(I:C) and CVB3 can stimulate the expression of type I IFN in OL cells by activating the TBK1–IRF3 pathway to express endogenous IFN-β. IFN-β activates the Janus kinase pathway, induces IRF7 expression by binding to the IFN receptor, and activates a new round of type I IFN expression, thus increasing antiviral activity [25]. In this study, our BDV nucleoprotein expression plasmid significantly inhibited type I IFN induction by poly(I:C) and CVB3 in OL cells. Similar results were observed in OL cells that overexpressed the BDV nucleoprotein that were then treated with IFN-β. It is clear that the BDV phosphoprotein can act as a competitive substrate to inhibit the function of TBK1 so that IRF3 and IRF7 cannot be activated and localised in the nucleus [16]. Our results show that the BDV nucleoprotein can also markedly inhibit IRF7 nuclear localisation, but the definite mechanism is unclear.

In summary, we have demonstrated that BDV nucleoprotein inhibits IRF7 activation through an unknown inhibitory mechanism and inhibits the induction of type I IFN, although the mechanism of inhibition needs further clarification. This study provides new evidence for understanding the interaction between BDV and host innate immune responses. BDV infection of specific cells can be used as an experimental model of wide type I IFN suppression to analyse natural immunity.

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