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Daunorubicin, a topoisomerase II poison, suppresses viral production of hepatitis B virus by inducing cGAS-dependent innate immune response

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ABSTRACT

Hepatitis B virus (HBV) causes hepatic diseases such as chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. These diseases are closely associated with persistent HBV infection. To prevent the progression of hepatic diseases, it is thus important to suppress persistent HBV infection. Daunorubicin (DNR), a topoisomerase II (Top II) poison, is a clinically used anticancer agent with a wide spectrum of activity against malignancies. DNR was recently reported to cause DNA damage-dependent interferon (IFN)-β induction through exogenous cyclic GMP-AMP synthetase (cGAS) and subsequently to suppress Ebola virus replication. In the present study, we demonstrated that DNR caused the inhibition of cell proliferation, but not cell death, through the DNA damage response in immortalized human hepatocyte NKNT-3/NTCP cells. Interestingly, DNR triggered the endogenous cGAS-dependent innate immune response and subsequently suppressed viral production of HBV in NKNT-3/NTCP cells. Top II poisons may be anti-HBV drug candidates.

1. Introduction

Hepatitis B virus (HBV) is a hepatotropic DNA virus belonging to the *Hepadnaviridae* family. Persistent HBV infection causes chronic hepatitis by inducing the host innate immune response and inflammatory response. Chronic hepatitis proceeds to liver cirrhosis and finally to hepatocellular carcinoma [1,2]. These hepatic diseases are closely associated with persistent HBV infection. To prevent the progression of hepatic diseases, it is thus important to suppress persistent HBV infection.

Topoisomerase II (Top II) is an important host factor for host DNA replication [3]. Top II unravels knots and tangles between the double helix of DNA by generating transient DNA double-stranded breaks (DSBs) which it subsequently re-ligates [3]. However, since the accumulation of DSBs causes cell cycle arrest, cell death, or apoptosis through the DNA damage response, both the expression level and the catalytic activity of Top II are regulated during the cell cycle [4,5].

Three Top II poisons—daunorubicin (DNR), doxorubicin (DOX), and teniposide (VM26)—are clinically used as anticancer agents with a wide spectrum of activity against malignancies [6]. These agents inhibit Top II-mediated re-ligation of transient DSBs in DNA and finally accumulate damaged DNA [7]. The damaged DNA is sensed by a host DNA damage sensor, the ataxia telangiectasia mutated (ATM) kinase in the nucleus, and subsequently causes G2/M cell cycle arrest through the DNA damage response mediated by its downstream effector, Chk2 [8]. Thus, these agents cause DNA damage responses through the activation of the ATM/Chk2 signaling pathway and finally through G2/M cell cycle arrest in normal cells. However, these agents are reported to cause mitotic cell death, presumably via deregulation of the cell cycle by the impairment of the G1 and/or G2 checkpoint in cancer cells [9].

On the other hand, DOX was previously reported to cause activation of the transcription factor interferon regulatory factor 3 (IRF-3) in human cervical carcinoma HeLa cells [10]. In addition, Luthra et al. recently reported that DOX and DNR also caused DNA damage-dependent interferon (IFN)-β induction through exogenous cyclic GMP-AMP synthetase (cGAS) and subsequently suppressed Ebola virus (RNA virus) replication [11]. cGAS is a host cytoplasmic DNA sensor that senses non-self-exogenous DNA such as viral DNA by recognizing their pathogen-associated molecular patterns [12,13].

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After sensing non-self-exogenous DNA, cGAS triggers innate immune responses such as the induction of IFN-β by activating IRF-3. Thus, Top II poisons trigger not only the DNA damage response but also the cGAS-dependent innate immune response.

HBV was recently reported to deregulate the cell cycle to promote viral replication and exhibit a premalignant phenotype in primary human hepatocytes [14]. In addition, we previously reported that HBV induced the cGAS-dependent innate immune response [15]. From these reports, we presumed that Top II poisons might suppress HBV by inducing mitotic cell death and/or the cGAS-dependent innate immune response in normal human hepatocytes. In the present study, we demonstrate that DNR, a Top II poison, triggers the cGAS-dependent innate immune response but not cell death, and subsequently suppresses the production of HBV in human immortalized hepatocyte NKNT-3/NTCP cells.

2. Materials and methods

2.1. Cell culture

Human immortalized hepatocyte NKNT-3 cells, which were kindly provided by N. Kobayashi and N. Tanaka (Okayama University), were cultured in the modified medium for human immortalized hepatocyte PH5CH8 cells [16]. NKNT-3/NTCP cells, which stably express exogenous NTCP, were maintained in the modified medium including blasticidin as described in our recently submitted paper [17].

2.2. Reagents

DNR and VM26 were purchased from Tokyo Chemical Industry (Tokyo). DOX was also purchased from Sigma-Aldrich (St. Louis, MO). Dimethyl sulfoxide (DMSO) was purchased from Nacalai tesque (Kyoto, Japan). Blasticidin was purchased from Funakoshi (Tokyo).

2.3. Cell count

NKNT-3/NTCP cells were plated onto 6-well plates (3.2×10^5 cells per well) and then treated with 1.0 μM of DNR for 12 h. At 0, 12, 24, and 48 h after treatment, the cells were harvested and then stained by trypan blue. Both living and dead cells were counted by a hemocytometer to evaluate the viability of DNR-treated NKNT-3/NTCP cells.

2.4. WST-1 cell proliferation assay

NKNT-3/NTCP cells were plated onto 96-well plates (0.8×10^4 cells per well) in duplicate and then treated with 0, 0.1, 0.5, or 1.0 μM of DNR for 12 h. At 0, 12, 24, and 48 h after treatment, we performed a WST-1 cell proliferation assay according to the manufacturer's protocol (Takara Bio, Kusatsu, Japan).

2.5. Quantitative RT-PCR analysis

Total cellular RNA was prepared by using an RNeasy Mini Kit (Qiagen, Hilden, Germany). cDNA was synthesized by using M-MLV reverse transcriptase (Invitrogen, Carlsbad, CA) and oligo dT primer (Invitrogen). TB Green Premix Ex Taq Kit (Takara Bio) and a real-time LightCycler PCR system (Roche Diagnostics, Basel, Switzerland) were used to perform quantitative RT-PCR analysis. The primer sets for IFN-β [18], IFN-λ1 [17], IFN-λ2/3 [17], IFN-γ [19], ISG56 [20], cGAS [15], and GAPDH [20] were used for quantitative RT-PCR analysis as previously described. We also prepared the following forward and reverse primer sets for ISG15: 5′-GCC TTCCAGCAGCGTCTGGC-3' (forward) and 5′-GCAGGCGCAGATTCAT GAACACGG-3' (reverse). The levels of IFN-β, IFN-γ, IFN-λ1, IFN-λ2/3, ISG15, ISG56, and cGAS mRNA were normalized by those of GAPDH mRNA. Data are the means ± SD from at least three independent experiments.

2.6. Western blot analysis

Cell lysates, sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and immunoblotting were prepared as previously described [21]. Anti-phospho-Chk2 (Thr68), anti-Chk2, anti-ISG56, anti-cGAS (Cell Signaling Technology, Beverly, MA), anti-ISG15 (H-150; Santa Cruz Biotechnology, Dallas, TX), and anti-β-actin (AC-15; Sigma-Aldrich) were used as primary antibodies. HRP-conjugated anti-mouse-IgG and anti-rabbit-IgG (Cell Signaling Technology) were used as secondary antibodies. Anti-β-actin antibody was used as a loading control.

2.7. RNA interference

Small interfering RNAs (siRNAs) targeting cGAS (MU-015607-01-0002; Thermo Fisher Scientific, Waltham, MA), Luciferase (D-001100-01-20; Thermo Fisher Scientific), or Cyclophilin B (D-001136-01-05; Thermo Fisher Scientific) were introduced into NKNT-3/NTCP cells by DharmaFECT transfection reagent (Thermo Fisher Scientific). One day after transfection of these siRNAs, NKNT-3/NTCP cells were treated with DNR for 12 h. At 48 h after treatment, total cellular RNA and the cell lysate were prepared from siRNA-introduced NKNT-3/NTCP cells. The knockdown effect of cGAS was evaluated in cGAS siRNA-introduced NKNT-3/NTCP cells by quantitative RT-PCR analysis and Western blot analysis. Luciferase siRNA or Cyclophilin B siRNA-introduced NKNT-3/NTCP cells were used as negative control.

2.8. Quantitative PCR analysis of HBV DNA

HBV inoculum was prepared from the supernatant of HepG2.2.15 cells [22] as previously described [15]. Quantitative PCR analysis was performed to measure the levels of intracellular and extracellular HBV DNA as previously described [15]. pUC19/C_JPNAT plasmid DNA was used as a standard to calculate the amounts of HBV DNA. Data are the means ± SD from at least three independent experiments.

2.9. Statistical analysis

The significance of differences among groups was assessed using Student's *t*-test. P values < 0.05 were determined to be statistically significant.

3. Results

3.1. DNR, a Top II poison, inhibits cell proliferation by inducing a DNA damage response in immortalized human hepatocyte NKNT-3/NTCP cells

We first examined whether DNR, a Top II poison, would induce cell death in immortalized human hepatocyte NKNT-3/NTCP cells. Using a trypan blue staining method, we measured cell viability at 0, 12, 24, and 48 h after treatment with DNR for 12 h (Fig. 1A). During the first 48 h after the DNR treatment, we observed no cytotoxicity in NKNT-3/NTCP cells (Fig. 1B). Top II poison causes a DNA damage response by inhibiting Top II-mediated re-ligation of transient DSBs in target DNA in normal cells. We next examined whether DNR induced a DNA damage response in NKNT-3/NTCP

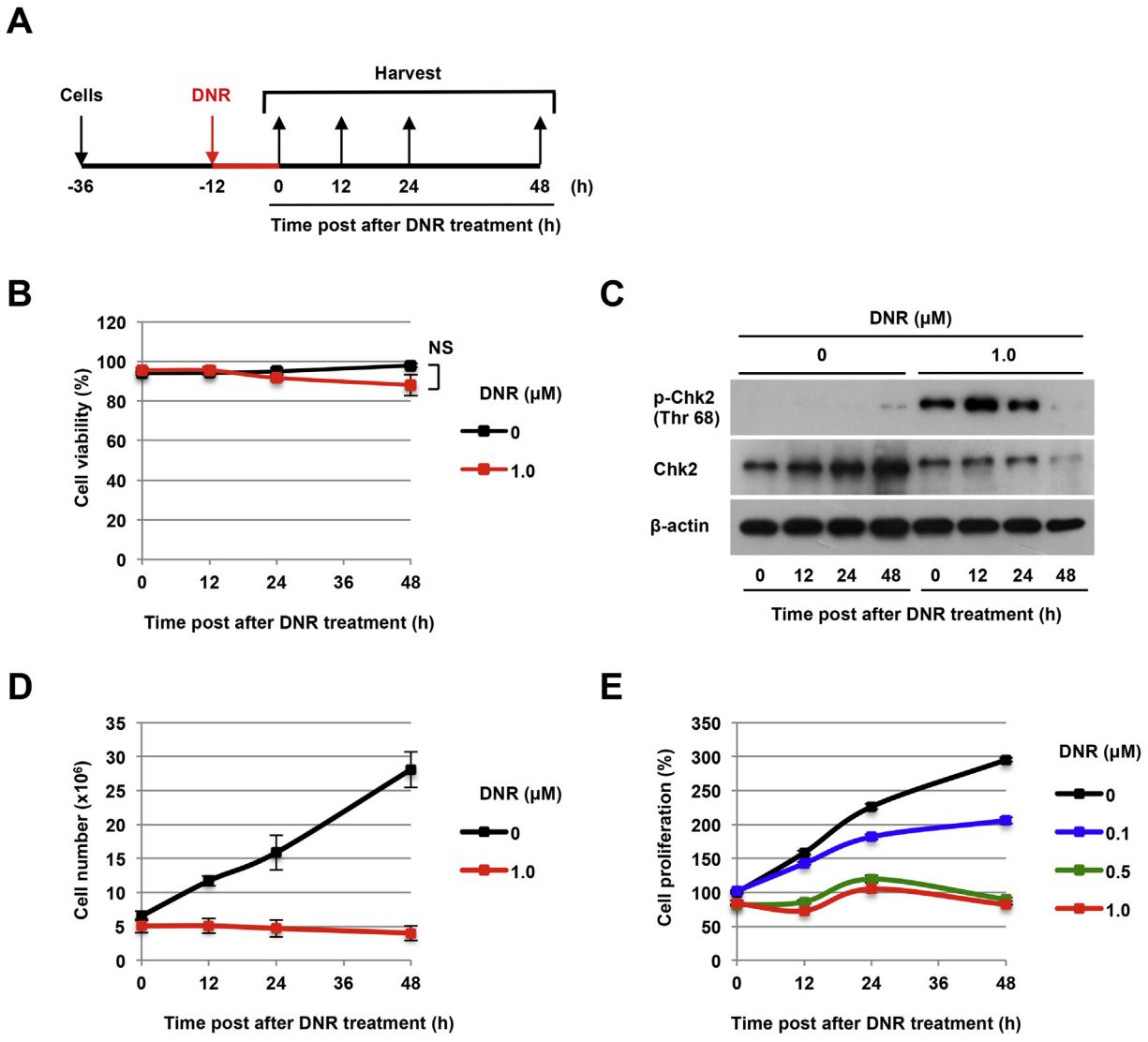

Fig. 1. DNR, a Top II poison, inhibits cell proliferation by inducing a DNA damage response in immortalized human hepatocyte NKNT-3/NTCP cells. (A) Scheme of DNR treatment in NKNT-3/NTCP cells. Cells were treated with DMSO or DNR for 12 h as shown by the red line and were harvested at each time point after DMSO or DNR treatment. (B) Viability of NKNT-3/NTCP cells at each time point after DNR treatment. The experiments were performed as described in Materials and methods. Data are the means ± SD from three independent experiments. NS: not significant. (C) Western blot analysis of phosphorylated Chk2 at Thr 68 in NKNT-3/NTCP cells at each time point after DNR treatment. Cell lysates were prepared as described in Materials and methods. (D) Number of NKNT-3/NTCP cells at each time point after DNR treatment. The experiments were performed as described in Materials and methods. Data are the means ± SD from three independent experiments. (E) WST-1 cell proliferation assay of NKNT-3/NTCP cells at each time point after DNR treatment. The experiments were performed as described in Materials and methods. Data are the means ± SD of three experiments in duplicate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cells. By Western blot analysis, we observed the phosphorylation of Chk2 at threonine 68 after the DNR treatment, suggesting that DNR caused the DNA damage response in NKNT-3/NTCP cells (Fig. 1C). Consistent with this result, both cell growth (Fig. 1D) and cell proliferation (Fig. 1E) were inhibited in NKNT-3/NTCP cells after the DNR treatment. These results suggest that DNR induces the DNA damage response and subsequently inhibits cell proliferation in NKNT-3/NTCP cells.

3.2. DNR triggers innate immune response in NKNT-3/NTCP cells

Since DNR was recently reported to cause DNA damage-dependent IFN-β induction [11], we next examined whether DNR also induced IFN-β in NKNT-3/NTCP cells. We obtained the results that DNR induced IFN-β mRNA in NKNT-3/NTCP cells in a dose- and time-dependent manner (Fig. 2A). Interestingly, as with IFN-β (type I IFN) mRNA, both IFN-γ (type II IFN) mRNA (Fig. 2B) and IFN-λ (type III IFN) mRNA (Fig. 2C) were also induced at 48 h after DNR treatment in NKNT-3/NTCP cells. We further demonstrated that DNR induced IFN-stimulated genes (ISGs) such as ISG15 and ISG56 in NKNT-3/NTCP cells (Fig. 2D and E). As with DNR, the two other Top II poisons, DOX and VM26, also induced ISG15 and ISG56 in NKNT-3/NTCP cells (Fig. 2F). These results suggest that Top II poisons trigger the innate immune response in NKNT-3/NTCP cells.

3.3. Endogenous cGAS is required for the DNR-triggered innate immune response in NKNT-3/NTCP cells

Both DNR and DOX were reported to cause DNA damage-dependent IFN-β induction in 293T cells transiently expressing exogenous cGAS [11]. We previously reported that cGAS was endogenously expressed in NKNT-3 cells [15]. From these results,

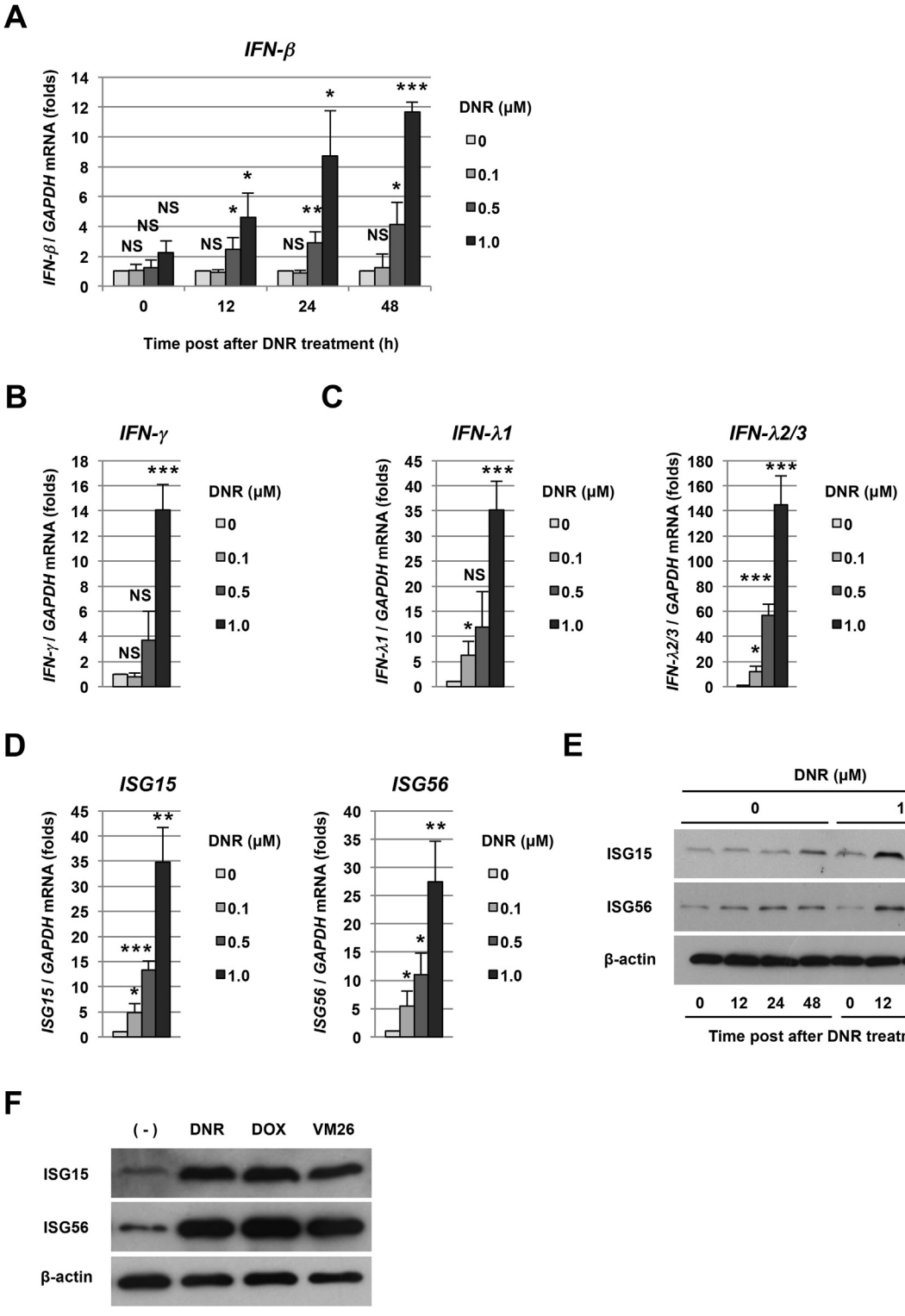

Fig. 2. DNR triggers innate immune response in NKNT-3/NTCP cells. (A) Quantitative RT-PCR analysis of IFN-β mRNA in NKNT-3/NTCP cells at each time point after DNR treatment. Total cellular RNA was prepared according to the scheme of the experiment as shown in Fig. 1A. Each mRNA level was calculated relative to the level in DMSO-treated NKNT-3/NTCP cells at each time point, which was set at 1. NS: not significant; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus DMSO-treated NKNT-3/NTCP cells at each time point. (B–D) Quantitative RT-PCR analysis of IFN-γ, IFN-λ1, IFN-λ2/3, ISG15, and ISG56 mRNA in NKNT-3/NTCP cells at 48 h after DNR treatment. Each mRNA level was calculated relative to the level in NKNT-3/NTCP cells at 48 h after DMSO treatment, which was set at 1. NS: not significant; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus DMSO-treated NKNT-3/NTCP cells. (E) Western blot analysis of ISG15 and ISG56 in NKNT-3/NTCP cells at 48 h after DNR treatment. The cell lysate was prepared as described in Fig. 1C. (F) Western blot analysis of ISG15 and ISG56 in NKNT-3/NTCP cells at 48 h after treatment with DNR, DOX, or VM26. Cell lysates were prepared from NKNT-3/NTCP cells at 48 h after DMSO-treatment or treatment with 1.0 μM of DNR, DOX, or VM26.

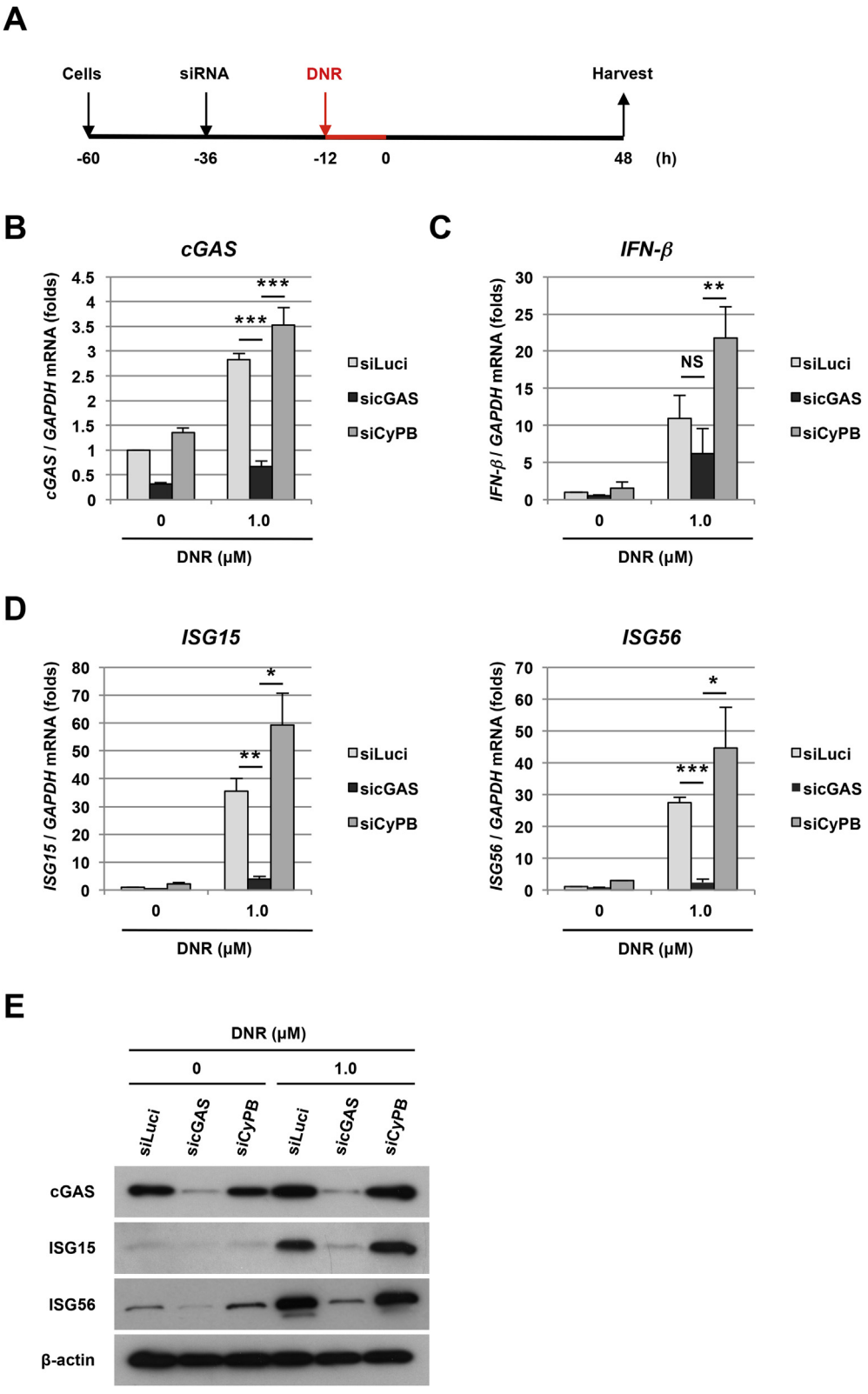

Fig. 3. Endogenous cGAS is required for DNR-triggered innate immune response in NKNT-3/NTCP cells. (A) Scheme of DNR treatment in NKNT-3/NTCP cells transfected with siRNA. Cells were transfected with Luciferase-specific (designated as siLuci), cGAS-specific (designated as sicGAS), or Cyclophilin B-specific (designated as siCyPB) siRNA, and then were treated with DMSO or DNR for 12 h as shown by the red line. At 48 h after DMSO or DNR treatment, cells were harvested. (B–D) Quantitative RT-PCR analysis of cGAS, IFN-β, ISG15, and ISG56 mRNA in each siRNA-transfected NKNT-3/NTCP cells at 48 h after DNR treatment. Each mRNA level was calculated relative to the level in DMSO-treated siLuci-transfected NKNT-3/NTCP cells, which was set at 1. NS: not significant; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. (E) Western blot analysis of cGAS, ISG15, and ISG56 in each siRNA-transfected NKNT-3/NTCP cells at 48 h after DNR treatment. The cell lysate was prepared as described in Fig. 1C.

we next examined whether endogenous cGAS was required for the DNR-triggered innate immune response in NKNT-3/NTCP cells (Fig. 3A). We obtained the results that RNAi-mediated knockdown of cGAS expression (Fig. 3B and E) reduced DNR-triggered induction of IFN-β (Fig. 3C), ISG15 (Fig. 3D and E), and ISG56 (Fig. 3D and E) in NKNT-3/NTCP cells. These results suggest that endogenous cGAS is required for the DNR-triggered innate immune response in NKNT-3/NTCP cells.

3.4. DNR suppresses HBV production by inducing cGAS-dependent innate immune response in NKNT-3/NTCP cells

Since NKNT-3/NTCP cells exhibited susceptibility to HBV [17], we next examined whether DNR suppressed HBV proliferation in NKNT-3/NTCP cells. According to the experimental scheme shown in Fig. 4A, we examined the effects of DNR in HBV-infected NKNT-3/NTCP cells. Consequently, we found that the DNR treatment significantly reduced extracellular HBV DNA at 48 h after DNR treatment for 12 h in HBV-infected NKNT-3/NTCP cells (Fig. 4B, right panel), although the levels of intracellular HBV DNA were significantly increased (Fig. 4B, left panel). These results suggest that DNR suppresses viral production rather than viral DNA replication against HBV in NKNT-3/NTCP cells.

4. Discussion

Top II is an important host factor for host DNA replication. DNA viruses, such as simian virus 40 (SV40) [23,24], herpes simplex virus type 1 (HSV-1) [25], adenovirus [26,27], and human cytomegalovirus [28,29], utilize host Top II probably for the release of the daughter strand during viral DNA replication. Therefore, previous reports suggested that the inhibition of Top II induced potent antiviral activity by blocking the release of the daughter strand. ICRF-193 (a Top II inhibitor), which prevents the release of Top II from DNA, blocked the viral DNA replication of SV40 [30] and of HSV-1 [31]. VM26 blocked viral DNA replication of human cytomegalovirus [29]. However, in the present study we did not observe DNR-blocking of HBV DNA replication in NKNT-3/NTCP cells (Fig. 4B, left panel).

On the other hand, Luthra et al. recently reported that DNR caused DNA damage-dependent IFN-β induction through exogenous cGAS and subsequently suppressed Ebola virus replication [11]. In our results, DNR also induced an endogenous cGAS-dependent innate immune response and significantly reduced extracellular HBV DNA in HBV-infected NKNT-3/NTCP cells (Fig. 4B, right panel). These results suggested that DNR prevented viral production rather than viral DNA replication against HBV by inducing a cGAS-dependent innate immune response.

Top II poisons are used clinically as anticancer agents against malignancies. On the other hand, these agents are known to exhibit side effects such as cardiotoxicity. DNR was reported to be less cardiotoxic than DOX in patients with childhood cancer [32]. Interestingly, the pegylated liposomal formulation of DOX, which reduces blood levels of DOX, is also clinically used for patients with

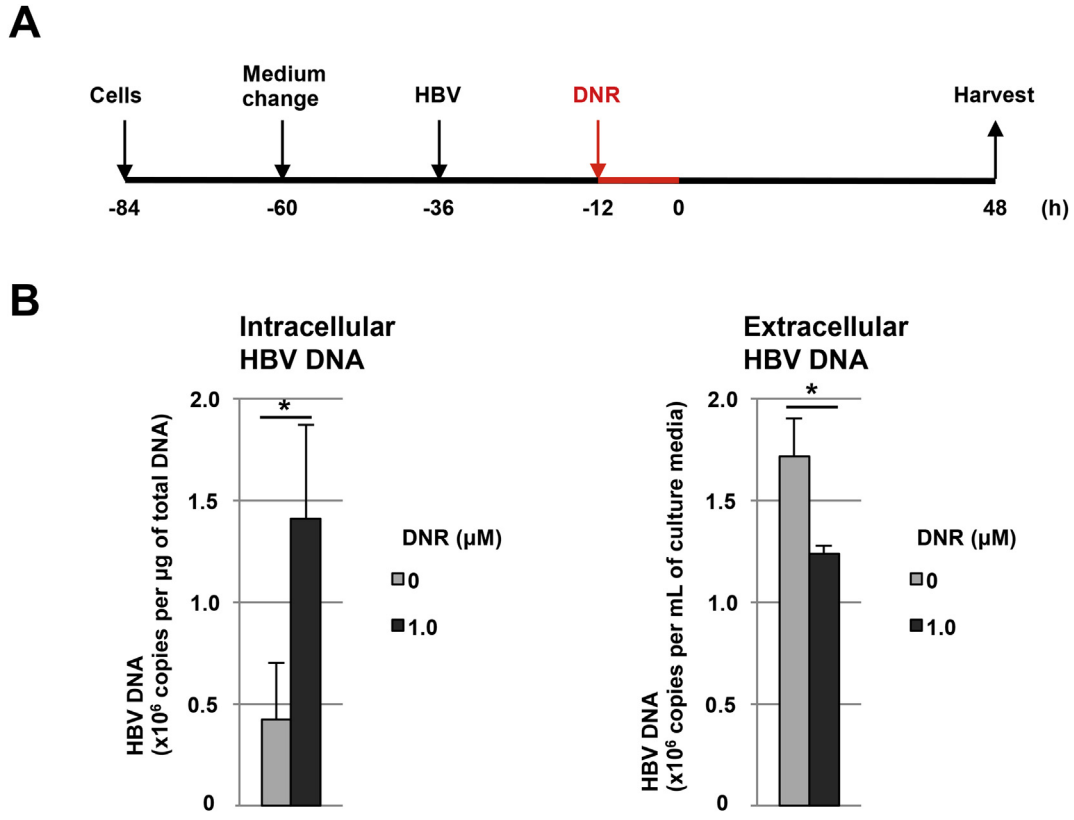

Fig. 4. DNR suppresses HBV production by inducing cGAS-dependent innate immune response in NKNT-3/NTCP cells. (A) Scheme of DNR treatment in HBV-infected NKNT-3/NTCP cells. Cells were inoculated with HBV as described in Materials and methods, and then were treated with DMSO or DNR for 12 h as shown by the red line. At 48 h after DMSO or DNR treatment, intracellular and extracellular DNA were prepared from HBV-infected NKNT-3/NTCP cells and their respective supernatants, respectively. (B) (left panel) Quantitative PCR analysis of intracellular HBV DNA in HBV-infected NKNT-3/NTCP cells at 48 h after DNR treatment. The total amount of intracellular HBV DNA was measured by quantitative PCR analysis. *$P < 0.05$. (right panel) Quantitative PCR analysis of extracellular HBV DNA released from HBV-infected NKNT-3/NTCP cells at 48 h after DNR treatment. The total amount of extracellular HBV DNA was measured by quantitative PCR analysis. *$P < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ovarian cancer and human immunodeficiency virus-associated Kaposi's sarcoma [33]. Since the pegylated liposomal formulation can relieve side effects by reducing blood levels of DNR, DNR may be effective in patients with HBV-associated hepatic diseases.

In conclusion, we have demonstrated that DNR, a Top II poison, suppresses viral production in HBV-infected human immortalized hepatocyte NKNT-3 cells.

Author contributions

HI, HD, and NK designed the research. HI performed most of the experiments. All authors analyzed the data. HI and HD wrote the paper. All authors reviewed the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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