Biochemical and Biophysical Research Communications 460 (2015) 555–560

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Identification of *APOBEC3B* promoter elements responsible for activation by human papillomavirus type 16 E6

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ARTICLE INFO

Article history:
Received 20 February 2015
Available online 20 March 2015

Keywords:
Human papillomavirus
E6
APOBEC3B
Promoter
ZNF384

ABSTRACT

Recent cancer genomics studies have identified mutation patterns characteristic of APOBEC3B (A3B) in multiple cancers, including cervical cancer, which is caused by human papillomavirus (HPV) infection. A3B expression is upregulated by HPV E6/E7 oncoproteins, implying a crucial role for A3B upregulation in HPV-induced carcinogenesis. Here, we explored the molecular mechanisms underlying the activation of the *A3B* promoter by E6. Luciferase reporter assays with a series of deleted fragments of the human *A3B* promoter in normal immortalized human keratinocytes (NIKS) identified two functional regions in the promoter: the distal region (from −200 to −51), which is required for basal promoter activity, and the proximal region (from +1 to +45), which exerts an inhibitory effect on gene expression. Each promoter region was found to contain an E6-resposive element(s). Disruption of an AT-rich motif located between +10 and +16 abrogated the proximal-region-mediated activation of the *A3B* promoter by E6. DNA pull-down assays revealed that a cellular zinc-finger protein, ZNF384, binds to the AT-rich motif in the *A3B* promoter, and chromatin immunoprecipitation assays confirmed that ZNF384 binds to the *A3B* promoter in cells. ZNF384 knockdown reduced the A3B mRNA levels in NIKS expressing E6, but not in the parental NIKS, indicating that ZNF384 contributes to *A3B* upregulation by E6, but not to basal *A3B* expression. The exogenous expression of ZNF384 led to the activation of the *A3B* promoter in NIKS. Collectively, these results indicate that E6 activates the *A3B* promoter through the distal and proximal regions, and that ZNF384 is required for the proximal-region-mediated activation of *A3B*.

1. Introducton

The apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family of proteins is a group of cellular enzymes that catalyze the deamination of cytidine (C) to uracil (U) in single-stranded DNA/RNA, and functions as antiviral factors in the innate immune system of the host [1]. In humans, the APOBEC family contains at least 11 members, including activation-induced cytidine deaminase and APOBEC1, -2, -3A, -3B, -3C, -3DE, -3F, -3G, -3H, and -4 [1]. The APOBEC proteins target not only viral DNA/RNA but also the host genomic DNA, generating enriched clusters of C-to-T conversions in the genome [2]. The expression of APOBEC3B (A3B) is upregulated in various human cancers, including cancers of the cervix, bladder, lung, head and neck, and breast [3–5]. Intriguingly, the overall level of C-to-T conversions in the cancer genome correlates positively with the level of A3B mRNA [3–5], implying an important role for A3B-mediated mutagenesis in the development of human cancers.

Persistent infections with a subset of human papillomaviruses (HPVs), called “high-risk HPVs”, including HPV16 and HPV18, are the primary cause of cervical cancer and some head-and-neck cancers [6]. HPV-induced carcinogenesis requires two viral oncoproteins, E6 and E7, which bind to and degrade p53 and Rb, respectively, thereby inhibiting these tumor suppressors and contributing significantly to the development of malignant cancer phenotypes [6].

Recent studies have demonstrated that E6/E7 of high-risk HPVs upregulate *A3B* expression [7–9]. Ohba et al. showed that HPV E6 and E7 individually activate the *A3B* promoter and the E6/E7-induced DNA double-stranded breaks are abolished by *A3B* knockdown [7]. This suggests that the mutagenic activities of E6/E7 are attributable to the induction of *A3B* expression. Furthermore, persistent infection with high-risk HPVs has been reported to upregulate *A3B* expression and promote APOBEC-mediated mutagenesis in head-and-neck cancers [9,10]. These results suggest a

Abbreviations: A3B, APOBEC3B; HPV, human papillomavirus; NIKS, normal immortalized human keratinocytes; HFK, human foreskin keratinocyte.

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http://dx.doi.org/10.1016/j.bbrc.2015.03.068
0006-291X/

crucial role for A3B activation by E6/E7 in HPV-induced carcinogenesis, although the mechanism underlying *A3B* promoter activation by E6/E7 remains unclear.

ZNF384 (also called CIZ/NMP4) is a zinc-finger protein that binds to the minor groove of AT-rich DNA. It functions as both a repressor and an activator of the transcription of several genes, including matrix metalloproteinase and type I collagen genes in osteoblasts [11–13].

We characterized the *A3B* promoter elements responsible for the activation of *A3B* expression by HPV16 E6 using reporter assays with a series of deletions and mutations in the *A3B* promoter. We report that E6 activates the *A3B* promoter through two promoter regions, the distal and proximal regions, and that ZNF384 is involved in the proximal-region-mediated activation of *A3B*.

2. Materials and methods

2.1. Cell culture

Normal immortal human keratinocytes (NIKS; American Type Culture Collection CRL-12191) and primary human foreskin keratinocytes (HFKs) (Kurabo, Osaka, Japan) were maintained on 3T3 feeder cells treated with mitomycin C, as described previously [14]. All experiments were performed with cells cultured in Keratinocyte-SFM (Life Technologies, Carlsbad, CA) supplemented with 30 μg/mL bovine pituitary extract and 0.2 ng/mL human recombinant epidermal growth factor.

2.2. Generation of E6-or E7-expressing cells

NIKS were stably transduced with a recombinant retrovirus expressing HPV16 E6 or E7, or the empty vector to produce NIKS-E6, NIKS-E7, or NIKS–V cells, respectively. The *E6* and *E7* genes were amplified by PCR from the HPV16 genome in W12 cells, and cloned into the retroviral transfer plasmid pMXs-puro (Cell Biolabs, San Diego, CA). Recombinant retroviruses were generated by the cotransfection of 293FT cells (Life Technologies) with pMXs-puro, pGP, and pE-ampho (Takara Bio, Shiga, Japan). NIKS were infected with the recombinant retroviruses and selected with 1 μg/mL puromycin, and the surviving cells were pooled. The expression of functional E6 in NIKS was confirmed with immunoblotting using an anti-p53 antibody (DO-1; Santa Cruz Biotechnology, Santa Cruz, CA). Immunoblotting was performed as previously described [15].

2.3. Plasmid construction

The *A3B* promoter region from nucleotide positions −500 to +45 (−500/+45) was amplified from the HFK genomic DNA with PCR using the primers: forward 5′-GAGCTCCACC-TAAGCCTTCCCTTGTG-3′, and reverse 5′-GCTAGCCTTAGA-TACGCTTGTCCCTG-3′. The numbering of the nucleotide positions is based on the Transcriptional Regulatory Element Database sequence (accession number: 28319) [16]. The PCR product was digested with *Sac*I and *Nhe*I, and inserted between the *Sac*I/*Nhe*I sites in the pGL3-Basic, a firefly luciferase reporter plasmid (Promega, Madison, WI), to produce pA3B–500/+45. Reporter plasmids with truncated *A3B* promoters were constructed similarly with PCR; plasmids containing nucleotides −200/+45, −50/+45, or −500/−1 were designated pA3B–200/+45, pA3B–50/+45, or pA3B–500/−1, respectively. A putative RUNX-binding sequence (ACCACAGA) in the *A3B* promoter was mutated to ACTATAGA with PCR and the corresponding region of pA3B–500/+45 was replaced with the mutated fragment to produce pA3B-RUNXm. An AT-rich motif (CAAAAAA) in the *A3B* promoter was similarly mutated to CGGGGAA to produce pA3B-ATm. The plasmid expressing ZNF384 (pCMV-ZNF384) was purchased from OriGene Technologies (Rockville, MD).

2.4. Luciferase reporter assay

NIKS-V and NIKS-E6 (5×10^4 cells/well) were grown in 24-well plates for 24 h and transfected with 450 ng of one of the luciferase reporter plasmids, together with 50 ng of pRL-null (Promega). To examine the effects of exogenous ZNF384 on the *A3B* promoter, the cells were cotransfected with 400 ng of reporter plasmid, 50 ng of pRL-null, and 50 ng of pCMV-ZNF384. Firefly and *Renilla* luciferase activities were measured 48 h after transfection, using the Dual-Luciferase Reporter Assay System (Promega) and a Mithras LB940 luminometer (Berthold Technologies, Bad Wildbad, Germany). The firefly luciferase activities were normalized to the *Renilla* luciferase activities.

2.5. DNA pull-down assay

A biotinylated DNA probe corresponding to −22/+45 in the *A3B* promoter was prepared with PCR using pA3B–500/+45 as the template and primers: forward 5′-biotin-GCTGTAAGCAGGAAGT-GAAA-3′ and reverse 5′-CTTAGATACGCTTGTCCCTG-3′. A DNA probe with mutations in the AT-rich motif was prepared with PCR, using pA3B-ATm as the template. The biotinylated DNA probe (1 μg) was coupled to 200 μg of Dynabeads M-280 Streptavidin (Dynal Biotech, Oslo, Norway) at room temperature for 30 min in buffer (10 mM Tris–HCl (pH 8.0), 0.5 mM EDTA, 1 M NaCl). Nuclear extracts were prepared from NIKS-V and NIKS-E6 using the Nuclear Extraction Kit (Affymetrix, Santa Clara, CA). The extract was diluted two-fold with Dulbecco's PBS (D-PBS) containing protease inhibitors (Complete, Roche Diagnostics, Indianapolis, IN), and 65 μg of the extracted protein was incubated with 200 μg of the DNA-coupled magnetic beads at 4 °C for 1 h. The beads were washed three times with D-PBS, and the bound proteins were eluted by boiling the beads in 20 μL of SDS sample buffer. The recovered proteins were analyzed with immunoblotting using anti-ZNF384 antibody (ab176689; Abcam, Cambridge, UK).

2.6. Chromatin immunoprecipitation (ChIP) assay

The ChIP assay was performed as described previously [17]. The antibodies used were the anti-ZNF384 antibody and normal rabbit IgG (Santa Cruz Biotechnology) as the negative control. The precipitated DNA was subjected to PCR to amplify the *A3B* promoter region (−100/+45) with the primers: forward 5′-TGAGCAG-GAATGGGGAGG-3′ and reverse 5′-CTTAGATACGCTTGTCCCTG-3′. The immunoprecipitated DNA was quantified with real-time PCR using SYBR® Green dye.

2.7. Small interfering RNA (siRNA) transfection

NIKS-V or NIKS-E6 (2×10^5 cells/well) were grown in six-well plates for 24 h and then transfected with 120 pmol of siRNA directed against ZNF384 (Dharmacon, Lafayette, CO) or control siRNA. Two days after transfection, the cells were harvested and analyzed with immunoblotting using the anti-ZNF384 antibody and anti-β-actin antibody (C-4; Santa Cruz Biotechnology) as the loading control.

2.8. Reverse transcription (RT)-quantitative PCR (qPCR)

The levels of A3B mRNA were measured with RT-qPCR using SYBR® Green dye. Total RNA was extracted from the cells with the RNeasy Mini Kit (Qiagen, Hilden, Germany) and 1 μg was reverse

transcribed to cDNA in a 20 μL reaction using the High Capacity RNA-to-cDNA Kit (Life Technologies). The total PCR reaction mixture (20 μL), containing 0.5 μL of cDNA solution, 10 μL of SYBR Green Realtime PCR Master Mix (Toyobo, Osaka, Japan), and 0.4 μM each primer, was subjected to real-time PCR on the LightCycler 480 (Roche Diagnostics). The amount of A3B mRNA was normalized to concurrently amplified glyceraldehyde phosphate dehydrogenase (GAPDH) mRNA. The nucleotide sequences of the primers for the A3B and GAPDH cDNAs have been described previously [18].

3. Results

3.1. Identification of E6-responsive element(s) in A3B promoter with reporter assays

We first generated NIKS stably expressing HPV16 E6 (NIKS-E6), E7 (NIKS-E7), or the selection marker alone (NIKS-V). The levels of A3B mRNA in these cells were quantified with RT-qPCR. The levels of A3B mRNA were significantly higher in NIKS-E6 and NIKS-E7 than in NIKS-V (Supplementary Fig. 1). Similar results were obtained for HFKs expressing E6 or E7 (Supplementary Fig. 1). These results are consistent with recent reports describing the upregulation of *A3B* expression by E6/E7 from high-risk HPVs [7–9]. Because E6 activated the expression of *A3B* more efficiently than E7, we focused our analyses on E6.

To identify the E6-responsive elements in the *A3B* promoter, we constructed a luciferase reporter plasmid (pA3B−500/+45) containing the human *A3B* promoter region from −500 to +45 (−500/+45), and a series of reporter plasmids with truncated *A3B* promoters (pA3B−200/+45, pA3B−50/+45, and pA3B−500/−1). NIKS-E6 and NIKS-V were transfected with these reporter plasmids, and their luciferase activities were measured 2 days after transfection. The levels of luciferase activity expressed from pA3B−500/+45 or pA3B−200/+45 were four-to six-fold higher in NIKS-E6 than in NIKS-V (Fig. 1A), indicating that the −200/+45 region contains an E6-responsive element(s). Further deletion (pA3B−50/+45) severely reduced the basal promoter activity in NIKS-V, and activation by E6 was reduced approximately two-fold, indicating that the −200/−51 region contains elements essential for basal *A3B* promoter activity and its E6-resposiveness. In contrast, deletion of the +1/+45 region (pA3B−500/−1) increased the basal promoter activity eight-fold compared with that of pA3B−500/+45, and activation by E6 was reduced approximately two-fold, indicating that the +1/+45 region exerts an inhibitory effect on *A3B* expression and contains another E6-responsive element(s). These results reveal two functional regions in the *A3B* promoter: the distal region (−200/−51), required for basal promoter activity, and the proximal region (+1/+45), which exerts an inhibitory effect on gene expression. Each region contains an E6-responsive element(s).

We examined the sequence of the −200/+45 region to identify transcription-factor-binding sites using the MAPPER search engine (http://genome.ufl.edu/mapper/). The distal region (−200/−51) contains putative binding sites for NF-κB, Sp1, and AP-1, whereas the proximal region (+1/+45) has a potential binding site for RUNX (Fig. 1B). The introduction of mutations into the RUNX-binding sequence (ACCACAGA to ACTATAGA in pA3B-RUNXm) slightly increased the luciferase activity in both NIKS-V and NIKS-E6, but did not affect the activation profile by E6 (Fig. 1A).

Interestingly, we found an AT-rich motif in the proximal region (Fig. 1B) that perfectly matches the consensus binding sequence ([G/C]AAAAA[A]) of the cellular zinc-finger protein ZNF384 [11]. Disruption of this AT-rich motif by mutation (CAAAAAA to CGGGGAA in pA3B-ATm) increased the luciferase activity to a level similar to that generated by pA3B−500/−1, and the level of promoter activation by E6 was reduced about two-fold (Fig. 1A).

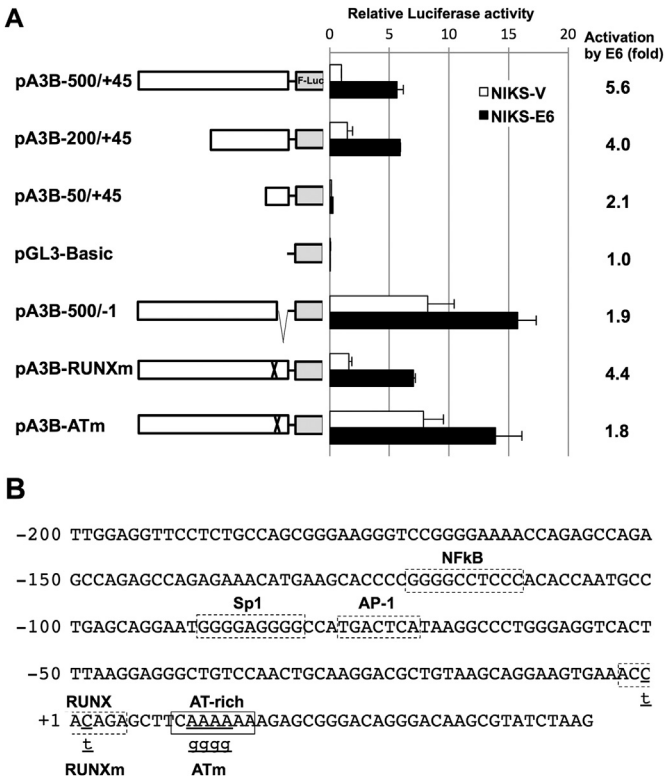

Fig. 1. Identification of E6-responsive element(s) in the *A3B* promoter with reporter assays. (A) NIKS-V and NIKS-E6 were transfected with the indicated firefly luciferase reporter plasmid together with the *Renilla* luciferase plasmid. Two days after transfection, the firefly and *Renilla* luciferase activities were measured and the firefly luciferase activity was normalized to the *Renilla* luciferase activity. The level of activation by E6 is shown as the fold change. Each bar represents the average of two independent experiments, with the standard error of the mean. (B) Nucleotide sequence of the −200/+45 region of the *A3B* promoter. The numbering of the nucleotide positions is based on the Transcriptional Regulatory Element Database sequence (accession number: 28319) [16]. The AT-rich motif (AT-rich) located between +10 and +16 is boxed. The putative transcription-factor-binding sites are boxed with dotted lines. The mutated sequences are underlined and the sequences in the mutants (RUNXm and ATm) are indicated below the sequence.

Therefore, the inhibitory effect of the proximal region on *A3B* expression is attributable to the AT-rich motif, which is also involved in the *A3B* promoter activation by E6, implying a potential role for ZNF384 in this activation.

3.2. ZNF384 binding to the A3B promoter

We tested whether ZNF384 recognizes the AT-rich motif in the *A3B* promoter, using DNA pull-down assays with nuclear extracts from NIKS-V and NIKS-E6. Similar levels of ZNF384 were detected in each nuclear extract, and ZNF384 was efficiently recovered from both nuclear extracts with a 67-bp DNA probe containing the −22/+45 sequence of the wild-type *A3B* promoter (Fig. 2A). In contrast, the same DNA probe mutated at the AT-rich motif (ATm) failed to associate with ZNF384, indicating that ZNF384 binds to the AT-rich motif sequence-specifically.

We next examined the binding of ZNF384 to the *A3B* promoter in living cells. In ChIP assays with an anti-ZNF384 antibody, the *A3B* promoter fragment (−100/+45) was enriched in the cross-linked chromatin fraction of NIKS-V and NIKS-E6 compared with the levels precipitated with the control antibody (Fig. 2B), indicating that ZNF384 associates with the *A3B* promoter in both NIKS-V and NIKS-E6. Notably, ZNF384 tended to bind to the *A3B* promoter more

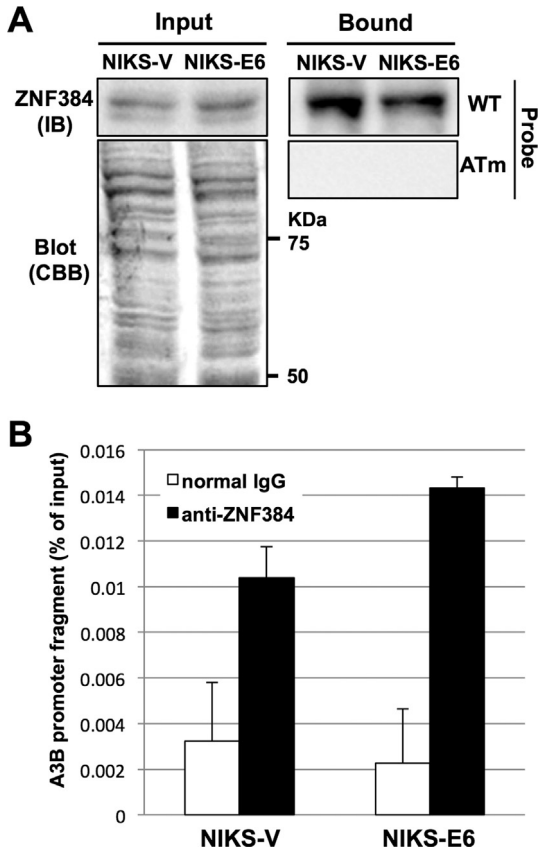

Fig. 2. ZNF384 binding to the *A3B* promoter. (A) A biotinylated DNA probe corresponding to the −22/+45 region of the wild-type (WT) or AT-rich motif mutant (ATm) sequence of the *A3B* promoter was coupled to Dynabeads M-280 Streptavidin, and incubated with the nuclear extract from NIKS-V or NIKS-E6. Part (25%) of the input fractions (Input) and 100% of the bound fractions (Bound) were analyzed by immunoblotting with anti-ZNF384 antibody. The Coomassie Brilliant Blue (CBB)-stained blot containing the input fractions is shown as the loading control. The data represent one of three independent experiments with similar results. (B) Cross-linked ZNF384/DNA complexes from NIKS-V and NIKS-E6 were immunoprecipitated with anti-ZNF384 antibody or normal rabbit IgG, and the immunoprecipitated DNA was subjected to PCR to amplify the *A3B* promoter fragment (−100/+45). The amounts of immunoprecipitated DNA were quantified with real-time PCR and are shown as percentages of the input DNA. Each bar represents the average of three independent experiments with the standard deviation.

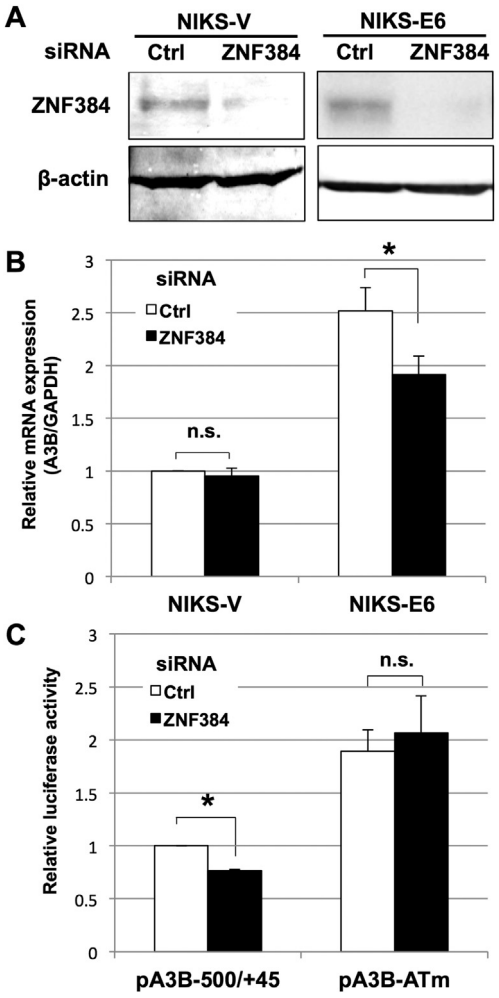

Fig. 3. Effects of ZNF384 knockdown on the E6-induced upregulation of *A3B*. (A) NIKS-V or NIKS-E6 were transfected with ZNF384 siRNA or control siRNA, and the cells were harvested 2 days after transfection and analyzed for the effects of knockdown by immunoblotting with anti-ZNF384 antibody. β-Actin was used as the loading control. (B) The levels of A3B mRNA in NIKS-V or NIKS-E6 transfected with ZNF384 siRNA or control siRNA were determined with RT-qPCR and normalized to the levels of GAPDH mRNA. The results are presented as the relative levels of the A3B mRNA compared with those in NIKS-V transfected with the control siRNA. (C) NIKS-E6 were cotransfected with the indicated firefly luciferase reporter plasmid, the *Renilla* luciferase plasmid, and either ZNF384 siRNA or control siRNA. Two days after transfection, the firefly and *Renilla* luciferase activities were measured and the firefly luciferase activity was normalized to the *Renilla* luciferase activity. Each bar in the graph represents the average of three independent experiments, with the standard deviation. The P value (* < 0.05; n.s. > 0.05) was calculated with Student's *t* test.

efficiently in NIKS-E6 than in NIKS-V, although the difference was not statistically significant (P > 0.05). Unexpectedly, and contrary to our expectation that ZNF384 binding to the AT-rich motif would repress the *A3B* promoter, these results suggest that ZNF384 binding to the *A3B* promoter enhances *A3B* expression.

3.3. Effects of ZNF384 knockdown on upregulation of A3B by E6

We then examined whether ZNF384 is involved in regulating the expression of the *A3B* gene, either by its activation or repression, using ZNF384 knockdown experiments. Transfection of siRNA directed against ZNF384 efficiently depleted the endogenous ZNF384 in NIKS-V and NIKS-E6 (Fig. 3A). ZNF384 knockdown did not affect the A3B mRNA levels in NIKS-V (Fig. 3B), indicating that ZNF384 is not required for basal *A3B* expression. In contrast, ZNF384 knockdown significantly reduced the A3B mRNA levels in NIKS-E6 (Fig. 3B). Furthermore, ZNF384 knockdown in NIKS-E6 reduced the luciferase activity expressed from the transfected reporter plasmid, pA3B−500/+45, but not that from pA3B-ATm (Fig. 3C). These results indicate that ZNF384 contributes to the upregulation of *A3B* expression by E6.

3.4. Activation of A3B promoter by exogenous ZNF384

The transactivation potential of ZNF384 was assessed with reporter assays during ZNF384 overexpression. Fig. 4A shows the levels of ZNF384 protein in NIKS-V transfected with plasmid expressing ZNF384 or the empty vector. ZNF384 overexpression led to a five-fold increase in luciferase activity from pA3B−500/+45 (Fig. 4B). Similarly, ZNF384 enhanced the luciferase activity from pA3B-ATm, but the level of activation was low (1.8-fold) compared with that from pA3B−500/+45, suggesting that the transactivation of *A3B* by ZNF384 largely depends on the intact AT-rich motif,

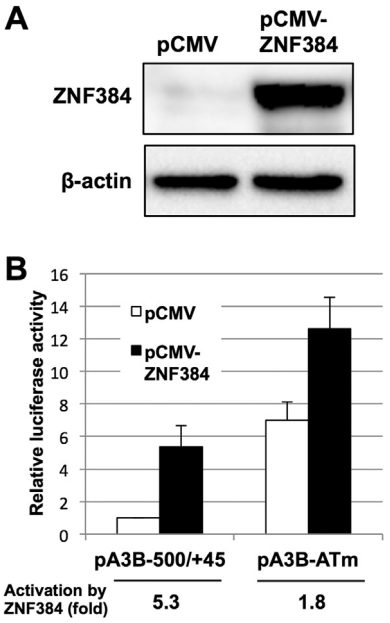

Fig. 4. Activation of the *A3B* promoter by exogenous ZNF384. (A) NIKS-V were transfected with a plasmid expressing ZNF384 (pCMV-ZNF384) or the empty plasmid (pCMV). The cells were harvested and analyzed for the expression of ZNF384 with immunoblotting using anti-ZNF384 antibody. β-Actin was used as the loading control. (B) NIKS-V were cotransfected with the indicated firefly luciferase reporter plasmid, the *Renilla* luciferase plasmid, and either pCMV or pCMV-ZNF384. Two days after transfection, the firefly and *Renilla* luciferase activities were measured and the firefly luciferase activity was normalized to the *Renilla* luciferase activity. The levels of activation by ZNF384 are shown as fold changes. Each bar in the graph represents the average of three independent experiments, with the standard deviation.

although there also seems to be some degree of AT-rich-motif-independent activation.

4. Discussion

In this study, we have shown that E6 activates the *A3B* promoter through two promoter regions, the distal and proximal regions, and that ZNF384 is required for the proximal-region-mediated activation (Figs. 1 and 3). Although ZNF384 is associated with the *A3B* promoter in NIKS-V (Fig. 2), it is not required for the basal expression of the *A3B* gene (Fig. 3B), suggesting that ZNF384 is not simply a transcription activator but functions as a modulator of *A3B* expression. Although the precise mechanism of the transcription inhibition mediated by the AT-rich motif is unclear at present, ZNF384 may alleviate the inhibitory effect of the AT-rich motif on *A3B* expression in the presence of E6.

In the distal region that mediates the activation of *AB3* by E6, we found putative binding sites for NF-κB, Sp1, and AP-1, and these transcription factors are reported to be activated by E6 [19–21]. Therefore, it is possible that these transcription factors are responsible for the basal *A3B* promoter activity, and that E6 activates the promoter by upregulating these transcription factors.

The induction of *A3B* by HPV16 E6 probably reflects a host defense mechanism against HPV infection. However, no negative impact on HPV16 replication was observed in W12 cells in which APOBEC3 expression was induced by interferon-β treatment, because the mutational load in the total viral population was extremely low [22]. Consequently, instead of eliminating HPV infection, the induction of *A3B* expression may present an unnecessary risk to the genomic integrity of the host, potentially promoting the development of cancer.

In a link to carcinogenesis, fusion proteins of ZNF384 and RNA-binding proteins, such as EWSR1 or TAF15, are often expressed in acute myeloid leukemia [23]. These fusion proteins have transforming properties in NIH3T3 cells [23,24], suggesting that ZNF384 has oncogenic potential as a fusion protein. Furthermore, ZNF384 overexpression in melanoma cells promotes metastasis [25]. ZNF384 is highly conserved from yeasts to humans, and is expressed in a variety of tissues [13], implying that this protein has essential, evolutionarily conserved, biological functions. Therefore, it is tempting to speculate that E6 affects various biological processes regulated by ZNF384, thereby further driving cervical carcinogenesis. More studies are required to clarify the molecular details of the E6-mediated activation of the *A3B* promoter, and to understand the roles of ZNF384 in the innate immune response and cancer development.

Conflict of interest

None.

Acknowledgments

We thank Dr. Tadahito Kanda for his critical reading of the manuscript and valuable comments on it.

This work was supported by a Grant-in-Aid for the Third-Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.03.068.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.03.068.

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