Biochemical and Biophysical Research Communications 435 (2013) 403–407

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

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

Histone deacetylases inhibitor trichostatin A modulates the extracellular release of APE1/Ref-1

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ARTICLE INFO

Article history:
Received 27 April 2013
Available online 9 May 2013

Keywords:
APE1/Ref-1
Trichostatin A
Secretion
Acetylation

ABSTRACT

Apurinic/apyrimidinic endonuclease 1/Redox factor-1 (APE1/Ref-1) can be acetylated via post-translational modification. We investigated the effect of an inhibitor of histone deacetylases on the extracellular release of APE1/Ref-1 in HEK293 cells. Trichostatin A (TSA), an inhibitor of histone deacetylases, induced APE1/Ref-1 secretion without changing cell viability. In a fluorescence quantitative assay, the secreted APE1/Ref-1 was estimated to be about 10 ng/mL in response to TSA (1 μM). However, TSA did not induce the secretion of lysine-mutated APE1/Ref-1 (K6R/K7R). TSA also caused nuclear to cytoplasmic translocation of APE1/Ref-1. Taken together, these findings suggest that APE1/Ref-1 is a protein whose secretion is governed by lysine acetylation.

1. Introduction

Apurinic apyrimidinic endonuclease 1/Redox factor-1 (APE1/Ref-1) is a multifunctional protein with a molecular weight of approximately 37 kDa. APE1/Ref-1 is involved in the base excision repair of abasic DNA lesions and eukaryotic transcriptional regulation [1]. These activities are located in 2 functionally distinct domains: (1) the N-terminus, which is principally devoted to redox activity and (2) the C-terminus, which functions as the rate-limiting endonuclease in the base excision repair pathway [2].

Most reports show that APE1/Ref-1 is localized in the nucleus, but growing evidence indicates that APE1/Ref-1 can be also localized in the cytoplasm, especially during high metabolic or proliferative states [1,3,4]. Mixed cytoplasmic and nuclear localization has also been reported [5–7], and APE1/Ref-1 undergoes an active shuttling between the cytoplasm and the nucleus in response to oxidative [8–10] or nitrosative stress [11]. Recent studies have reported many nuclear and extra-nuclear functions of APE1/Ref-1 [12].

Localization of APE1/Ref-1 is controlled by the first 20 amino acids at the N-terminal sequence [13]. APE1/Ref-1 is acetylated by the p300 histone acetyl transferase (HAT) [9]. In addition, lysines 6 and 7, at the N-terminus of APE1/Ref-1, serve as acetyl acceptor residues and are targeted for deacetylation by histone deacetylases (HDAC) [14,15]. Furthermore, HDAC was identified as an APE1/Ref-1 nuclear export inhibitory protein [11]. Lysine acetylation occurs on histone tails, but it can also occur on many non-histone proteins [16]. Lysine acetylation has been linked to the compartmentalization and secretion of specific target proteins. For example, lysine acetylation of high-mobility group protein-1 (HMG-1) leads to its secretion [17]. Another example is acetylation-mediated cytoplasmic accumulation of the nuclear viral protein E1A [18]. Secretome 2.0 [19,20], a software to predict secreted proteins, identified APE1/Ref-1 as a non-classically secreted protein. The aim of this study was, therefore, to determine whether APE1/Ref-1 can be secreted and to explore the role of lysine acetylation in APE1/Ref-1 secretion.

2. Materials and methods

2.1. Reagents

Trichostatin A (TSA), nicotinamide, and butyrate were obtained from Sigma–Aldrich (St. Louis, MO, USA). Tissue culture medium and fetal bovine serum (FBS) were obtained from Invitrogen. Protease and phosphatase inhibitor cocktails were purchased from Roche Applied Science (Indianapolis, IN, USA). The antibody against APE1/Ref-1 was obtained from Abcam (Cambridge, MA, USA). Anti-β-actin and FLAG-tag antibodies were from Sigma–Aldrich. Anti-acetylated lysine antibody and anti-acetylated lysine agarose beads were purchased from Cell Signaling Technology (#9441,

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http://dx.doi.org/10.1016/j.bbrc.2013.04.101

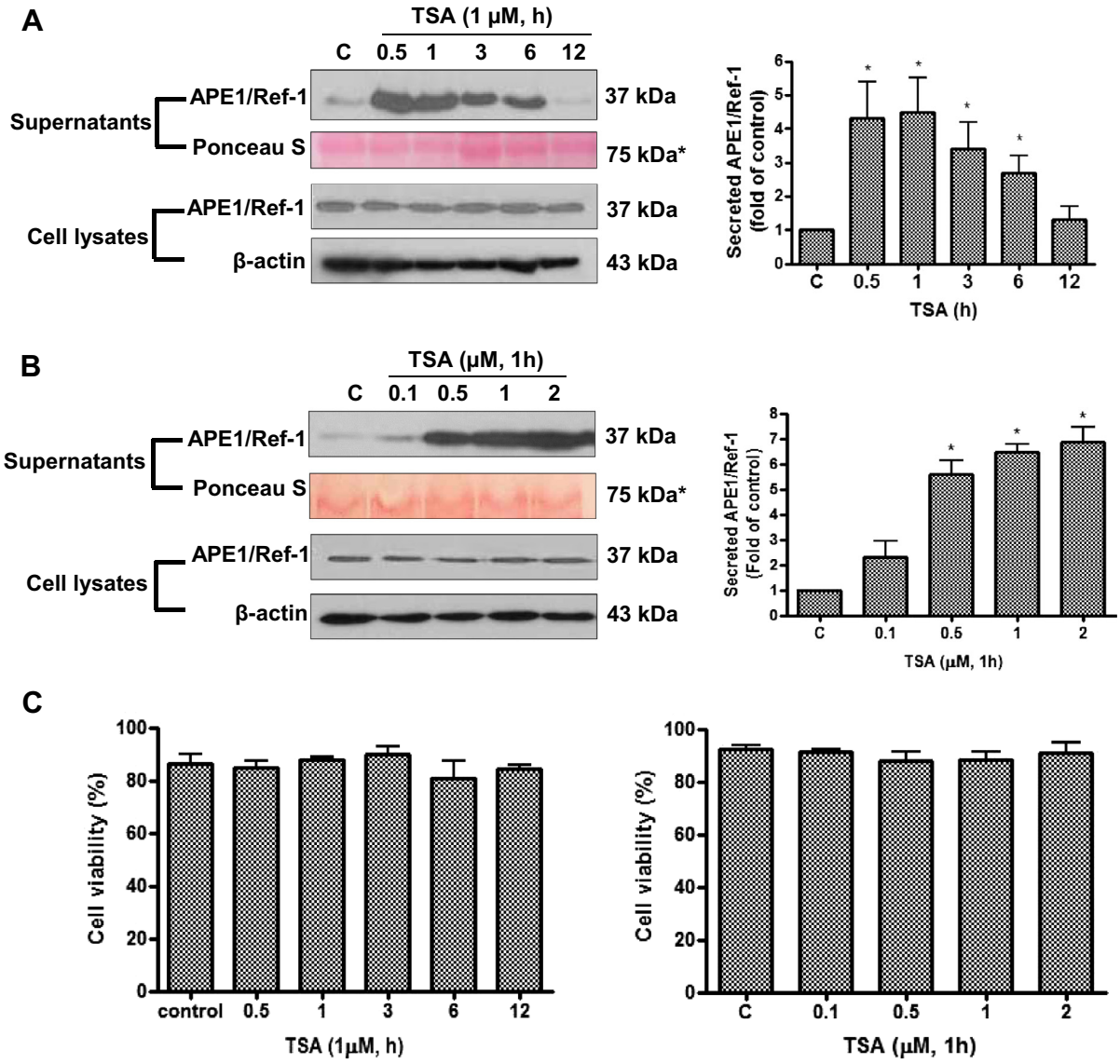

Fig. 1. Tricostatin A (TSA) induced the secretion of APE1/Ref-1 in HEK293 cells. (A) Time course of TSA on APE1/Ref-1 secretion in HEK293 cells. After cells were treated with TSA (1 μM) for the indicated times, acetone precipitation and Western blotting was performed for the supernatant of the culture medium. *A 75 kDa unknown protein demonstrated by Ponceau S staining and β-actin were used as a control to show the equal protein loading for precipitated proteins and the cell lysate, respectively. Summarized data was plotted in Fig. 1A. Each bar shows the mean ± SEM ($n = 4$). *$p < 0.05$ *vs.* control. (B) Dose dependence of TSA on APE1/Ref-1 secretion in HEK293 cells. After cells were treated with TSA (0.1–1 μM) for 1 h, acetone precipitation and Western blotting was performed for the supernatant of the culture medium. *A 75 kDa unknown protein demonstrated by Ponceau S staining and β-actin were used as a control to show the equal protein loading for precipitated proteins and the cell lysate, respectively. Summarized data for Fig. 1A. Each bar shows the mean ± SEM ($n = 4$). *$p < 0.05$ *vs.* control. (C) The effect of TSA on cell viability in HEK293 cells. Cell viability was determined by an automatic cell counter (ADAM-MC) using AccuChip^{4x} Kit (Digital Bio, Seoul, Korea). Each bar shows the mean ± SEM ($n = 3$). Note that cell viability was unaffected by TSA (1 μM) for 0–12 h or TSA for 1 h at concentrations of 0.1–2 μM.

Beverly, MA, USA) and Immunechem (#ICP0388, Burnaby, BC, Canada), respectively.

2.2. DNA constructs

Human APE1/Ref-1 cDNA was cloned into pCMV-Tag2A (BD Biosciences Clontech, USA) to generate plasmid pCMV-APE1/Ref-1. pFLAG-hAPE1/Ref-1 (K6R/K7R mutant) has been previously described [15].

2.3. Cell culture and viability assay

The human embryonic kidney epithelial (HEK293) cell line was maintained in Dulbecco's Modified Eagle's Medium (Welgene, Korea) with 10% fetal bovine serum (Gibco, Carlsbad, CA, USA) and 1% antibiotics. Cells were maintained in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C. The effect of the TSA treatment on cell viability was determined by propridium iodide fluorescent staining using an automatic cell counter (ADAM-MC) using AccuChip^{4x} Kit (Digital Bio, Seoul, Korea) [21].

2.4. Pull-down of secretory APE1/Ref-1

Secretory APE1/Ref-1 in the culture supernatant was chemically pull-downed. Proteins in the culture supernatant were precipitated in cold acetone at four times the volume of the supernatant for 1 h at −20 °C. The supernatant was centrifuged at 15,000×*g* for 10 min. Subsequently, the protein pellets were dried at room temperature for 30 min and resuspended in a 25 μl buffer containing 20 mM Tris–HCl (pH 7.5) and 1% Triton X-100. Each sample was mixed with a sample buffer and subjected to SDS–PAGE, which was followed by immunoblotting using anti-APE1/Ref-1.

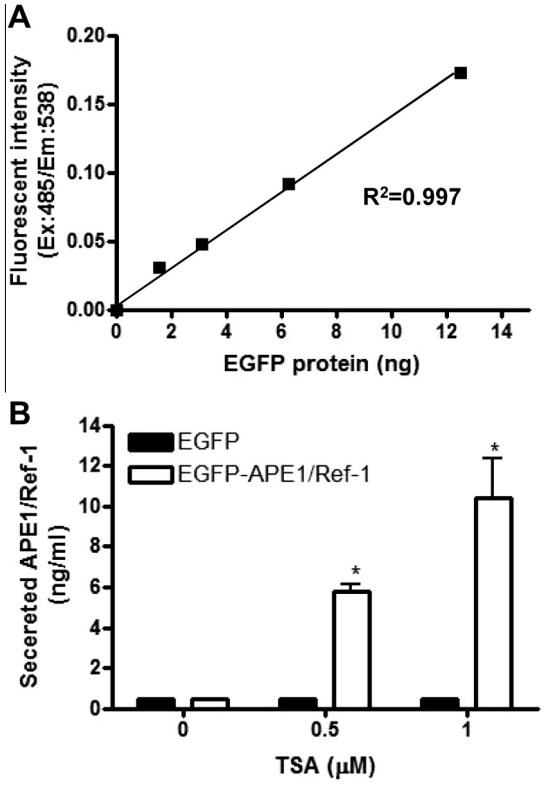

Fig. 2. Quantitative analysis of TSA-induced APE1/Ref-1 secretion. (A) Standard curve of EGFP was prepared by using a known amount of recombinant EGFP proteins with the linear portion ranging 1.5–12 ng of the recombinant EGFP. (B) Estimation of secreted EGFP-APE1/Ref-1 protein induced by TSA. Note that the exposure of TSA (0.5, 1 μM for 1 h) increased APE1/Ref-1 in supernatants of EGFP-APE1/Ref-1-transfected cells, but not in EGFP-transfected cells. Each bar shows the mean ± SEM ($n = 4$). $^{*}p < 0.05$ *vs.* basal.

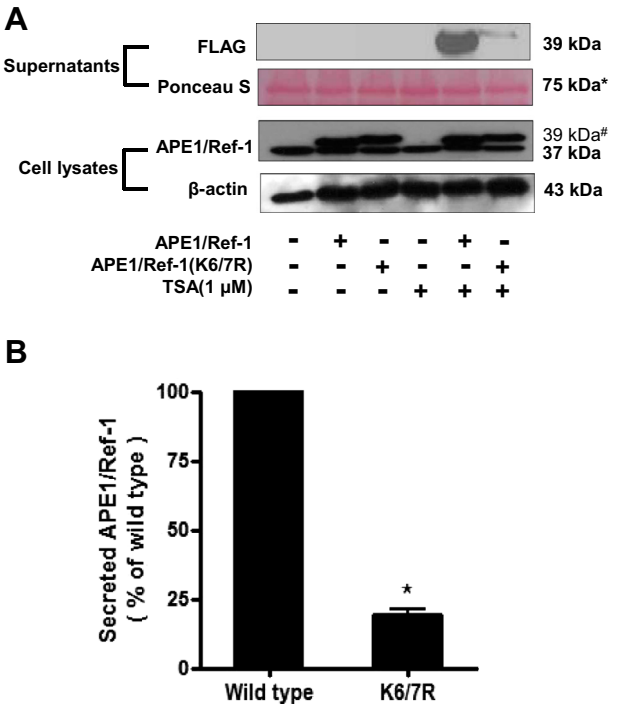

Fig. 3. APE1/Ref-1 secretion depends on the acetylation of K6/K7 residues (A) TSA-induced APE1/Ref-1 secretion was suppressed by the lack of significant acetylation with K6R/K7R. APE1/Ref-1 secretions were measured in the supernatants of cells, which were transfected with FLAG-tagged lysine mutant (K6R/K7R) and FLAG-tagged APE1/Ref-1. *A 75 kDa unknown protein demonstrated by Ponceau S staining and a β-actin were used as a controls to show the equal protein loading for precipitated proteins and the cell lysate, respectively. (B) Summarized data for TSA-induced APE1/Ref-1 secretion in the supernatants of cells, which were transfected with the FLAG-tagged wild type and lysine mutant (K6R/K7R). Each bar shows the mean ± SEM ($n = 3$). $^{*}p < 0.05$ *vs.* wild-type of Flag-APE1/Ref-1.

2.5. Immunoblotting

Cells were harvested on ice by using a lysis buffer, 20 mM Tris HCl (pH 7.5), 0.5% NP 40, 250 mM NaCl, 3 mM EDTA, 2 mM DTT, 10 mM nicotinamide, 10 mM butyrate, 5 μM TSA and protease inhibitors. The homogenates were cleared by centrifugation at 14,000×*g* for 15 min and the supernatant proteins were obtained. The supernatants were precipitated and then used for determination of protein concentration. Prepared proteins were resolved by 10% SDS–PAGE and transferred onto a polyvinylidene difluoride membrane. After blocking with 5% nonfat dry milk in Tris-buffered saline, the membrane was incubated with the desired primary antibody overnight at 4 °C. The membrane was then treated with an appropriate secondary antibody, and the immunoreactive bands were visualized using an enhanced chemiluminescence method (Pierce Biotechnology, Rockford, IL, USA). As a protein loading control, each membrane was stained with Ponceau S (Sigma) or re-probed with an anti-β-actin antibody to normalize for differences in transfer and protein loading. Changes in APE1/Ref-1 protein levels were assessed by densitometric scanning of the immunoreactive bands.

2.6. Purification of recombinant EGFP

Recombinant EGFP protein was purified from a pET28/EGFP expression system [22], and the isolated EGFP was then purified under native conditions. In brief, following 4 h of induction with IPTG, cells were sonicated in a buffer solution (500 mM NaCl, 50 mM Tris, pH 8.0). The recombinant protein was purified on a Ni–NTA agarose column (Qiagen). After washing with a 50 mM imidazole containing buffer solution, EGFP proteins were eluted from a 250 mM imidazole containing buffer solution followed by desalting with a PD-10 column (Amersham Pharmacia Biotech) into a phosphate buffered saline (PBS). Purified proteins were aliquoted and stored in a liquid nitrogen tank until use.

2.7. Immunocytochemical analysis of APE1/Ref-1

HEK293 cells were cultured on coverslips and treated with TSA. After washing with PBS, cells were fixed with 4% paraformaldehyde and permeabilized with 0.1% Triton X-100. The cells were incubated with normal goat serum (1:20 dilution) in PBS for 45 min. Cells were then treated with an anti-APE1/Ref-1 antibody (1:600 dilutions) overnight at 4 °C. The cells were washed with bovine serum albumin buffer (0.5% bovine serum albumin, 0.15% glycine in PBS) and incubated with an Alexa Fluor 488-conjugated secondary antibody (1:1000 dilutions, Molecular Probes) for 1 h. After washing, nuclei were counterstained with propidium iodide (PI, 5 μg/mL) for 3 min.The cells were visualized under a fluorescent microscope.

2.8. Statistical analysis

All data are expressed as the mean ± SEM. Statistical significance of differences in measured variables between the control and TSA-treated groups was determined by using an one-way ANOVA followed by Dunnett's or Bonferroni's test for multiple comparisons. Differences were considered significant at $P < 0.05$.

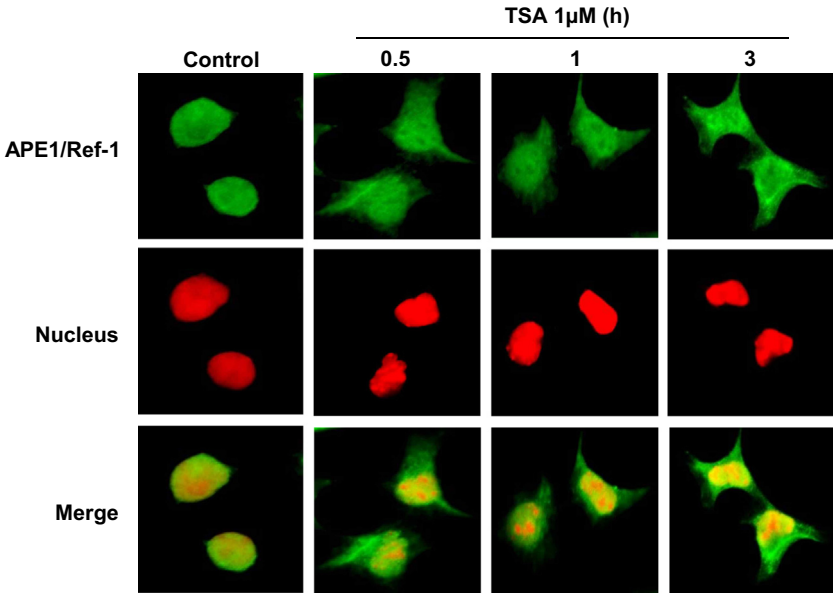

Fig. 4. Cytoplasmic translocation of APE1/Ref-1 by TSA treatment in HEK293 cells. Exposure of TSA (1 μM) for 0.5, 1 and 3 h causes a significant relocation of APE1/Ref-1 to the cytoplasm. Cells were fixed with 4% paraformaldehyde and permeabilized with 0.1% Triton X-100. They were immunostained with anti-APE1/Ref-1 (Green, Alexa 488) and propridium iodide (Red) for nucleus staining. Magnification, 400×. Similar results were observed in experiments run in triplicate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Inhibition of deacetylation stimulates APE1/Ref-1 secretion

Post-translational modification of protein is one important component leading to protein secretion [14]. We investigated whether APE1/Ref-1 is a secreted protein and if its secretion is governed by acetylation. APE1/Ref-1 in supernatants of HEK293 cells was analyzed by Western blotting. As shown in Fig. 1A, APE1/Ref-1 was detectable in supernatants, and the magnitude of secreted APE1/Ref-1 increased significantly with the exposure of cells to the HDAC inhibitor TSA. APE1/Ref-1 in supernatants reached peak levels at 1 h and returned to baseline at 12 h of TSA (1 μM). However, intracellular APE1/Ref-1 expression was unchanged by TSA. The exposure of TSA (0.1–2 μM for 1 h) increased APE1/Ref-1 in supernatants in a dose-dependent manner (Fig. 1B). However, TSA did not affect cell viability as demonstrated by propridium iodide assay (Fig. 1C). Taken together, these data indicate that APE1/Ref-1 is a secreted protein and its secretion is stimulated by the inhibition of HDAC activity.

3.2. Secretion of EGFP-APE1/Ref-1

To estimate how much APE1/Ref-1 is secreted into the medium, we measured the effect of TSA on the change of fluorescence in a culture medium of EGFP-APE1/Ref-1-transfected cells. The secreted EGFP-APE1/Ref-1 protein in the supernatant was estimated by comparison with an EGFP standard curve. As shown in Fig. 2A, the standard curve of EGFP was prepared by using a known amount of recombinant EGFP proteins with a linear portion ranging 1.5–12 ng of the recombinant EGFP. The exposure of TSA (0.5, 1 μM for 1 h) increased the fluorescent intensity in supernatants of EGFP-APE1/Ref-1-transfected cells. With an estimation of secreted EGFP-APE1/Ref-1, with the value as the standard with EGFP protein, TSA (0.5, 1 μM for 1 h) induced the secretion of 5.8 ± 0.4 and 10.4 ± 2.0 ng/mL of EGFP-APE1/Ref-1. However, TSA did not affect EGFP secretion in EGFP-transfected cells.

3.3. Role of acetyl-acceptor lysine residues in APE1/Ref-1 secretion

To identify the role of acetyl-acceptor lysine residues in APE1/Ref-1 secretion, APE1/Ref-1 secretion was examined in cells transfected with a non-acetylatable form of APE1/Ref-1 (K6R/K7R). Compared to wild-type APE1/Ref-1, TSA-stimulated secretion of APE1/Ref-1 (K6R/K7R), that was non-acetylatable on lysines 6 and 7, was markedly diminished to 19.2 ± 2.2% (Fig. 3). This indicates that acetylation of K6/K7 plays an important part in APE1/Ref-1 secretion.

3.4. Inhibition of deacetylase promotes cytoplasmic translocation of APE1/Ref-1

To determine whether acetylation affected in cellular compartmentalization of APE1/Ref-1, the effect of TSA on the localization of endogenous APE1/Ref-1 was examined. In control cells, APE1/Ref-1 was mainly localized in the nuclei of HEK 293 cells (Fig. 4). After exposure to TSA, there was a significant shift in APE1/Ref-1 from the nucleus to the cytoplasm, indicating that the inhibition of HDACs leads to the cytoplasmic translocation of APE1/Ref-1.

4. Discussion

This study demonstrated that the exposure of HDAC inhibitor TSA promotes APE1/Ref-1 secretion into the medium of cultured cells without a significant loss of cell viability. APE1/Ref-1 secretion is strongly associated with intracellular acetylation, particularly with K6/K7 acetylation.

Post-translational protein modification is a crucial mechanism in regulating protein function in eukaryotic cells. Similar to other post-translational modifications, protein acetylation exerts pleiotropic effects on its target protein. Histone deacetylases (HDACs) may act as intra-nuclear gatekeepers based on their ability to antagonize NO-induced APE1/Ref-1 trafficking [11]. TSA, a specific inhibitor of HDAC, enhances the acetylation levels of many proteins [23]. APE1/Ref-1 is acetylated by the P300/CBP-associated factor, also known as lysine acetyl transferase, and deacetylated

by Class I HDACs, histone deacetylases inhibitor TSA induced the acetylation of APE1/Ref-1 [9].

Our findings indicate that TSA stimulates APE1/Ref-1 secretion, suggesting that intracellular acetylation provokes APE1/Ref-1 secretion. This is further supported by the finding that TSA does not stimulate secretion of APE1/Ref-1 (K6R/K7R), which is non-acetylatable on lysines 6 and 7. Therefore, acetylation of the K6/K7 residue of APE1/Ref-1 has a key role in APE1/Ref-1 secretion in response to TSA. Exposure of HEK293 cells to 1 μM TSA did not affect cell viability as determined by propidium iodide staining. The presence of APE1/Ref-1 in the supernatants, as shown in the immunoblot, was not due to cell death. It was also confirmed by the absence of a reactive band with the anti-β-actin antibody on the same membrane (data not shown). Therefore, APE1/Ref-1 could be secreted or leaked out by intracellular acetylation.

APE1/Ref-1 is a 37 kDa nuclear protein containing nuclear localization signals. As the 20 N-terminal residues of APE1/Ref-1 implicate the nuclear localization signal peptide for nuclear translocation, the APE1/Ref-1 mutants lacking the nuclear localization signals would be localized outside of the nucleus [13]. In the present study, as shown by immunocytochemical analysis, endogenous APE1/Ref-1 is transported to the cytoplasm in response to TSA for 1 h. As acute exposure to TSA for 1 h has a limited ability to induce de novo APE1/Ref-1 protein expression, increased cytoplasmic APE1/Ref-1 by TSA must be due to the cytoplasmic translocation of APE1/Ref-1. Our results provide evidence that acetylation of APE1/Ref-1 occurs in the cytoplasmic translocation of APE1/Ref-1. Recently, it was confirmed that the protein kinase C activator increased cytoplasmic APE1/Ref-1, suggesting the cytoplasmic translocation of APE1/Ref-1 in endothelial cells [24].

Lysine acetylation of proteins regulates major cellular functions as a common post-translational modification of proteins and it could play a pivotal role in the signaling pathways [25]. Intracellular acetylation is closely associated with vascular inflammation such as atherosclerosis [26,27]. As HDACs are promising target protein for therapy in cardiovascular disease, HDAC inhibitors have important implications for the potential application in cardiovascular disorders [28]. Therefore, the detection of extracellular APE1/Ref-1 can be used as good biomarkers for intracellular acetylation in cardiovascular disorders. The existence of extracellular APE1/Ref-1 can lead to further study aiming to extracellular functions of APE1/Ref-1 or cytokine-like functions of APE1/Ref-1. Also our data would provide the necessary knowledge for understanding of the extracellular trafficking of intracellular protein in response to HDAC inhibition. Taken together, our data showed that APE1/Ref-1 can be secreted in response to HDAC inhibitor, and the lysine acetylation of APE1/Ref-1 acts as a key mechanism for APE1/Ref-1 secretion.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2011-0006231, 2011-0016797 and 2012R1A1A3015385).

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